Charles University

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Study program: Chemistry

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Application of enantioselective allylation for synthesis of compounds isolated from *Streptomyces gramineus*

Aplikace enantioselektivní allylace pro syntézu látek izolovaných z *Streptomyces gramineus*

Diploma Thesis

Supervisor: Prof. RNDr. Martin Kotora, CSc.

Prague, 2020

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 15.6. 2020

Podpis

ABSTRACT

E-492, actinofuranone A, and JBIR-108 are natural compounds isolated from actinobacteria *Streptomyces* genus and can lead to the development of new pharmaceuticals as they have some biological interesting activities. Although the synthesis of these actinofuranones has been already published, this work brings new methods for the preparation of their fragments. The key step of the synthesis is enantioselective crotylboration of an aldehyde catalyzed by a chiral Brønsted acid and by which two centres of chirality are introduced in one step. The other crucial steps of the synthesis are composed of Ru-catalyzed alkene-alkene cross-metathesis and Pd-catalyzed Suzuki cross-coupling.

Keywords: natural compound, enantioselective syntheses, crotylation, catalysis, actinofuranone fragment

ABSTRAKT

E-492, aktinofuranon A a JBIR-108 jsou přírodní látky izolované z aktinobakterií rodu *Strepromyces* a vzhledem k jejich biologické aktivitě mají potenciální význam ve farmacii. Přestože syntéza těchto fragmentů byla již publikována, tato práce přináší novou metodu přípravy jejich fragmentů. Stěžejním krokem této syntézy je enantioselektivní krotylace aldehydu Brønstedovou kyselinou, při které vzniká homoallylický alkohol se dvěma novými centry chirality. Mezi další klíčové kroky této syntézy patří zkřížená metateze dvou alkenů katalyzovaná rutheniovým katalyzátorem a paladiem katalyzovaný Suzukiho cross-coupling.

Klíčová slova: přírodní látky, enantioselektivní syntéza, krotylace, katalýza, aktinofuranonový fragment

CONTENT

LIST OF ABBREVATIONS

Ac	acetyl
app	apparent
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2-naphthol
br	broad
Bu	butyl
d	doublet
dppf	1,1'-bis(diphenylphosphino)ferrocene
CAB	chiral acyloxy borane
Cbz	carboxybenzyl
Cp	cyclopentadienyl
dd	doublet of doublet
ddd	doublet of doublet of doublet
dt	doublet of triplet
ESI	electrospray ionization
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
ee	enantiomeric excess
er	enantiomeric ratio
HG II	Hoveyda-Grubbs catalyst of 2nd generation
HPLC	high-performance liquid chromatography
HMPA	hexamethylfosforamid
HRMS	high resolution mass spectrometry
IC	inhibitory concentration
Ipc	isopinocampheyl
IR	infrared
LA	Lewis acid

LB	Lewis base
m	multiplet
Me	methyl
MS	mass spectrometry
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetyl
NMR	nuclear magnetic resonance
PA	phosphoric acid
Ph	phenyl
PTC	phase transfer catalyst
n-Pr	propyl
q	quatet
rt	room temperature
s	singlet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
td	triplet of dublet
THF	tetrahydrofuran
TLC	thin-layer chromatography
TRIP-PA	3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
UV	ultraviolet

1 INTRODUCTION

Enantioselective synthesis is a chemical process in which is (are) generated center(s) of chirality and the final compound is preferentially formed in one enantiomer. Enantioselective synthesis is the crucial tool of modern chemistry as the enantiomers or diastereoisomers often have different properties. Demand for the enantiomerically pure compounds is increasing not only from the pharmaceutical companies but also from other fields of chemistry as agrochemicals, food additives and special materials.[1]

Enantioselective synthesis can be achieved by many techniques such as: 1) using chiral starting material, 2) by resolution of two enantiomeric products or 3) by a reaction that is catalyzed by a chiral compound. The first option has rather limited possibilities as only a limited selection of chiral compounds like L-amino-acids and D-sugars is available. The second option is economically non-effective as usually only one enantiomer is further used. The third option has shown to be an effective way how to synthesize the chiral compound, but one of the drawbacks is that the catalyst is usually not very general and even small changes in a substrate's structure may lead to the change of the catalyst effectiveness.

Allylation is one of the reactions that leads to the formation of new a centre of the chirality at carbon atom and has drawn the interest of many research groups lately. It has been studied under many different conditions with various reagents and its research including natural compound synthesis is still growing. Contrary to allylation reaction, the use of enantioselective crotylation reaction in the synthesis of a natural compound is rather unexplored.

Polyketides as JBIR-108,[2] actinofuranone A[3] and E-492[4] (Figure 1) are natural secondary metabolites that were isolated from bacteria of the genus *Streptomyces*. Due to their biological activity, they are potential therapeutics. This diploma thesis focuses on a total enantioselective synthesis of three fragments: a) the C7-C18 of E-492, b) the C7-C18 of actinofuranone A and c) the C7-C20 of JBIR-108. It is an extension of my bachelor thesis where the synthesis of the racemic fragment C7-C18 of E-492 was achieved.

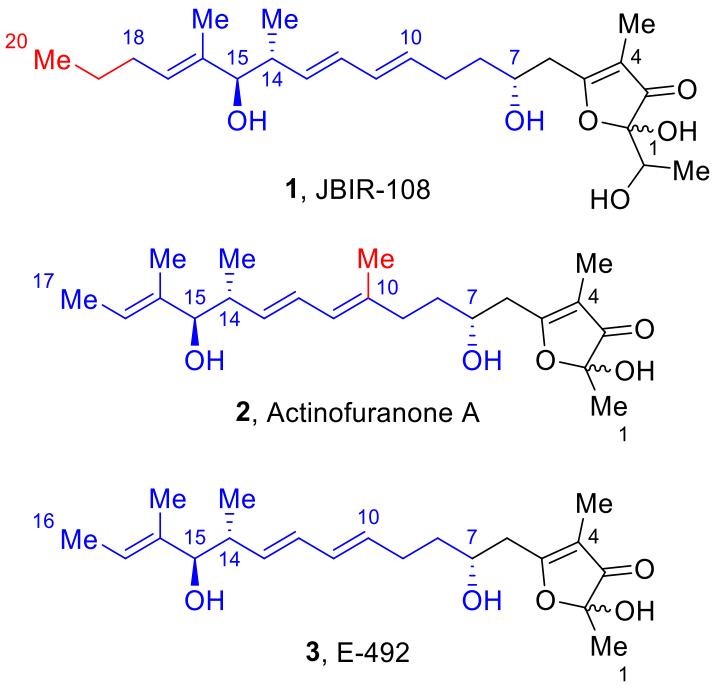
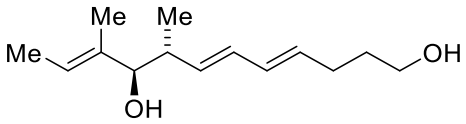


Figure 1. Compounds isolated from *Streptomyces* genus.

2 AIMS OF THE WORK

1. Screening of the enantioselective crotylation in the first step of the synthesis of fragments **4**, **5**, and **6** with the chiral Brønsted acid TRIP-PA.

2. Enantioselective synthesis of C7-C18 fragment of E-492 **4**.



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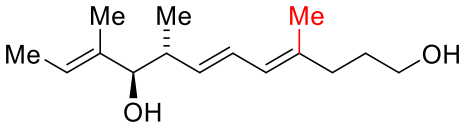
3. Modification of the synthetic route for the preparation of fragments C7-C18 of actinofuranone A **5** and C7-C20 of JBIR-108 **6**.



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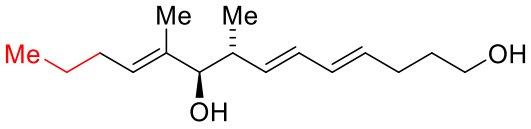

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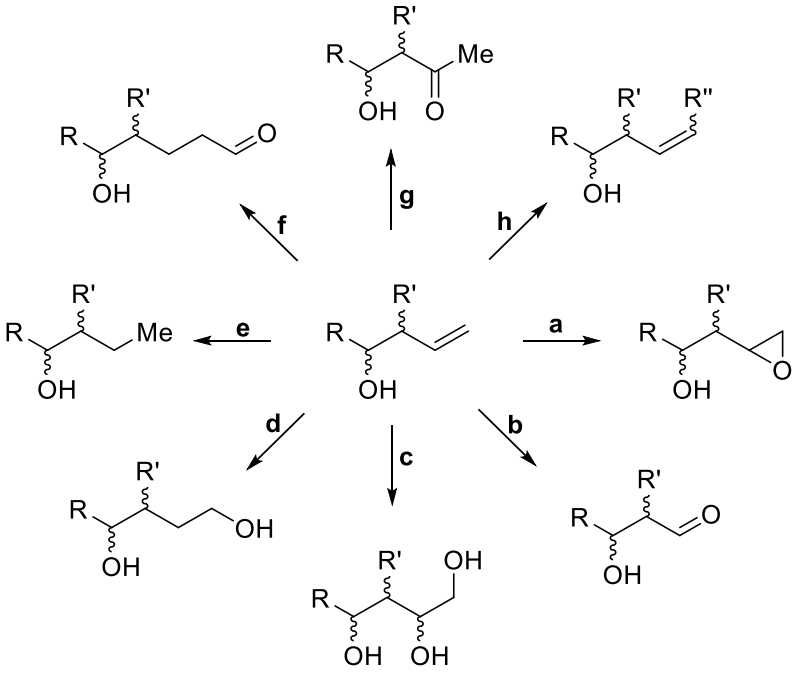
3 STATE OF THE ART

3.1 Enantioselective Crotylation

The formation of new bonds between carbon atoms is a useful synthetic process and has always drawn attention of organic synthetic chemists. This stems from the fact that extension or enlargement of the molecular framework is an important operation for the synthesis of complex molecules from a simple starting material.

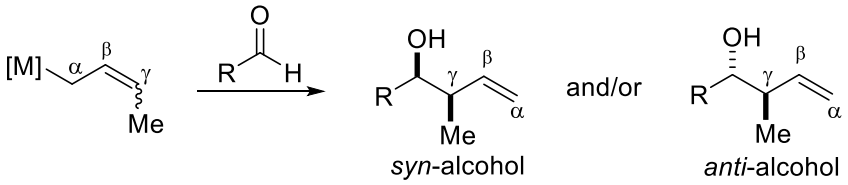
Allylation or crotylation is an important method in organic synthesis for extension of the carbon chain via formation of a new C–C bond. It results in the formation of methylhomoallylic alcohols that are important building blocks in the synthesis of various natural compounds or pharmaceuticals as the double bond of the allyl/crotyl group can be further used for various synthetical transformation such as: a) epoxidation, b) ozonolysis, c) dihydroxylation, d) hydroboration/oxidation, e) hydrogenation, f) hydroformylation, g) Wacker oxidation, h) Heck coupling[5] or olefin metathesis (Scheme 1).



Scheme 1. Possible double bond transformation.

The crotylation reaction itself is an addition of crotyl nucleophiles to an electrophile. The crotyl group, $-CH_2CH=CHCH_3$, is a functional group that exists in two double bond stereoisomers (*E* and *Z*) and the reaction can proceed either at α or γ position. The γ-carbon

addition is a very interesting reaction in organic synthesis because in the case of enantioselective variant two new centers of chirality are formed in the molecule (Scheme 2).

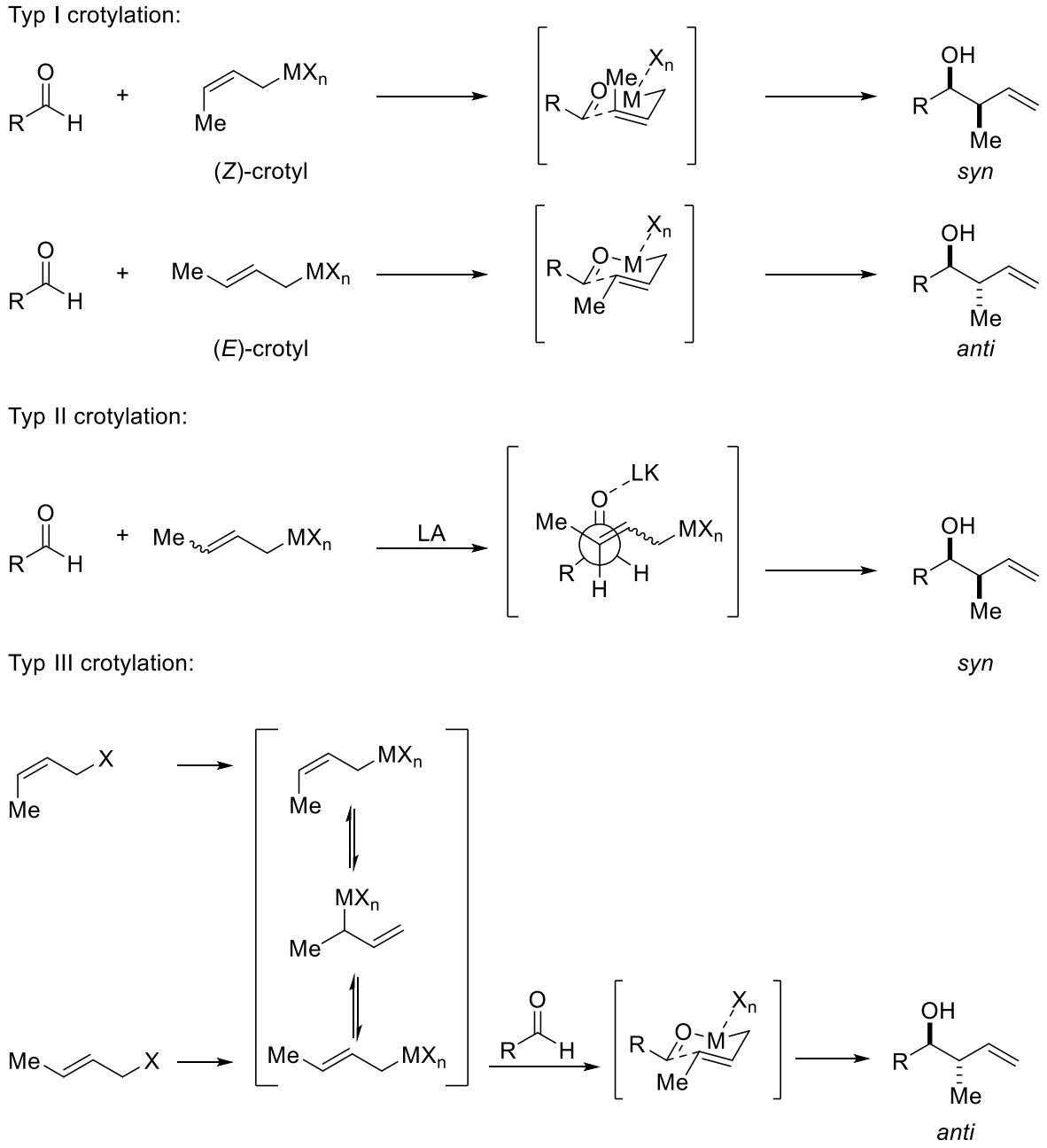


Scheme 2. Crotylation of aldehydes.

Enantioselective crotylation can either proceed through a chair-like transition state or an open transition state. Denmark has classified the enantioselective crotylation reaction into three types (Scheme 3).[6] The Type I is the addition of a crotyltrichlorosilane catalyzed by Lewis bases (LB). The reaction mechanism proceeds via a closed chair-like transition state and reflects the *Z*/*E* ratio of the starting crotyl reagent to give the corresponding *syn* or *anti*-product.

Type II is the addition of an organometallic crotylic reagent (Si, Sn, or B) catalyzed by a Lewis acid (LA) and gives predominantly *syn*-products independently of the double bond geometry in the starting crotylic reagent. The Lewis acid activates an aldehyde toward a nucleophilic attack. The reaction mechanism proceeds via an open transition state to form the *syn* product.

The third type is based on the reaction of crotylic organometallic reagents (Cr, Zn, In) that are generated *in situ* from corresponding crotyl halides. This reaction proceeds via the closed chair-like transition state and gives predominantly *anti*-products regardless of the starting double bond geometry.



Scheme 3. Three types of enantioselective crotylation according to Denmark.

3.2 Methods of Crotylation

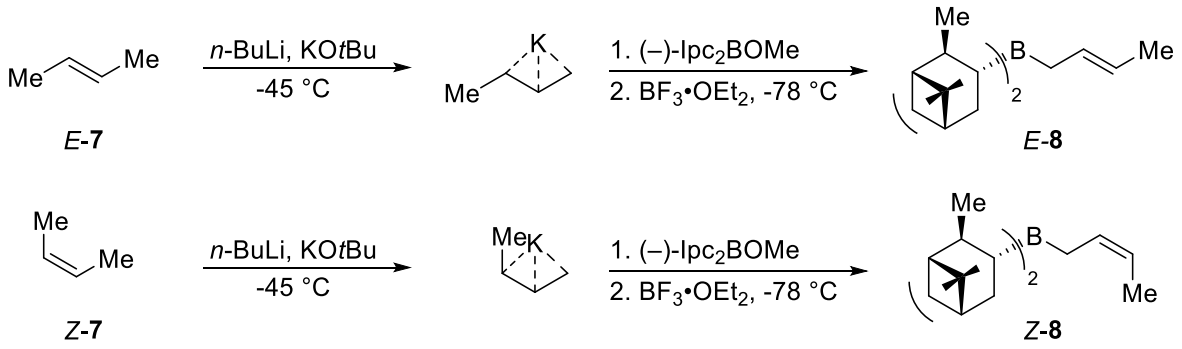
Preparation of non-racemic alcohols through allyl- or crotyl- addition to aldehydes has been studied for more than three decades and it has undergone important evolution since Hoffmann's pioneering study.[7] He observed that the relative stereochemistry can be controlled by the bond geometry of allyl/crotyl reagents. He used chiral allyl boronic esters, prepared from a chiral glycol, to get the product with 45-77% ee depending on the aldehyde. Since then, the effort to find an ideal reagent for this type of reaction continues.

According to Leighton, the allylation reagent should be a) easily prepared in both enantiomeric forms, b) stable and easily stored and utilized through trivial procedures, c) user- and environment-friendly, d) effective and lead to high enantioselectivity. Besides, it would be beneficial if it could be: e) easily recyclable, f) insensitive to reaction temperature, g) highly selective with chiral substrates and h) easily modifiable to the more complex allylic system.[8,9] Many allylation reactions have been discovered by Corey[10], Panek[11], Chong,[12] Keck,[13] Carerra[14,15] or crotylation to ketones by Shibasaki,[16] Schauss.[17,18]

I would like to highlight in this work only the reagents that have been studied within the context of the crotylation of aldehydes.

3.2.1 Stoichiometric Chiral Reagents

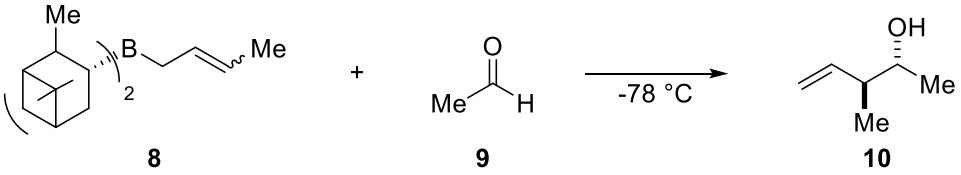
Chemoselective, diastereoselective and enantioselective crotylation was first investigated by using the stoichiometric amount of a chiral crotyl reagent. Brown's discovery of highly enantioselective crotylation using pinane-derived reagents dates to early 1980s (Scheme 4).[19] He synthesized the chiral crotyl reagent from but-2-ene using Schlosser base condition for the allylic deprotonation to stabilize the *E*/*Z* configuration followed by the reaction with methoxydiisopinocampheylborane (derived from (+)-, (−)-α-pinene).



Scheme 4. Syntheses of Brown's crotyl reagent.

He was able to perform the crotylation reaction of the reagent **8** with acetaldehyde to get all four homoallylic alcohols stereoisomers with a high enantioselectivity (90-92% ee) (Table 1).[20]

Table 1. Brown's crotylation.



8 **9** **10**

Ipc_2BOMe from	K salt from	Yield (%)	Configuration	ee (%)
(+)-α-pinene	(*Z*)-but-2-ene	75	2*R*, 3*R*	90
(+)-α-pinene	(*E*)-but-2-ene	78	2*R*, 3*S*	90
(−)-α-pinene	(*Z*)-but-2-ene	72	2*S*, 3*S*	92
(−)-α-pinene	(*E*)-but-2-ene	76	2*S*, 3*R*	92

The scope of stoichiometric chiral crotyl reagents has been later extended. Roush used (−)-diethyl tartrate ester of boronic acid **11** as a chiral moiety,[21–23] Masamune 2,5-dimethylborolanes **12**,[24] and Soderquist[9] prepared his chiral reagent through an air-stable pseudoephedrine borinic ester complexes **13** (Figure 2). Not only boron-based reagents have been studied in stoichiometric crotylation, but also other organometallic reagents based on silicon and titanium. Leighton reagents **14** and **15** can be easily synthesized by a reaction of crotyltrichlorsilanes with corresponding diamines.[25,26] He overcame the limitation of the substrate scope by using LA, especially $Sc(OTf)_3$, and broadened the methodology even to less reactive aldehydes such as unsaturated and sterically hindered ones.[27] Duthaler has achieved the preparation of a crotyl reagent based on the titanium **16** by the reaction of the cyclopentadienylchlorotitanium complex with but-1-ene under the Schlosser conditions.[28]

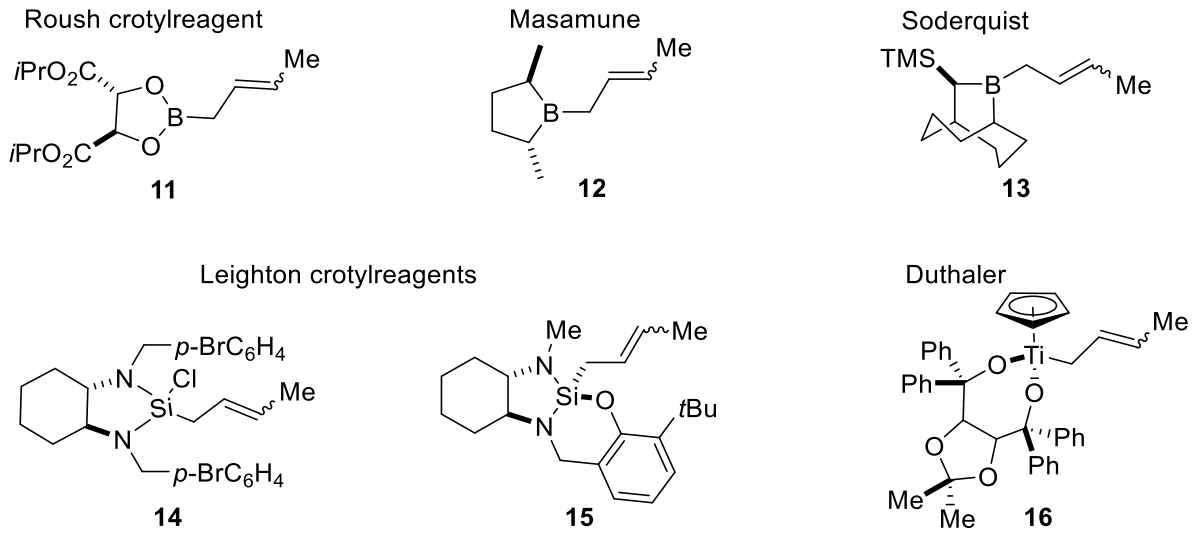
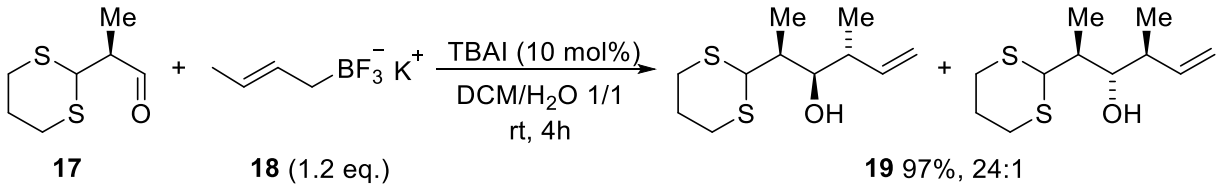


Figure 2. Types of stoichiometric crotyl reagent.

Crotylation in aqueous media. Diastereoselective crotylation of aldehydes in aqueous environment was studied with potassium crotyltrifluoroborate. The crotylation in biphasic system DCM/H_2O was published for the first time by Batey. He used Bu_4NI as a phase transfer catalyst (PTC) to get high yields (≥ 94%) and excellent diastereoselectivity (dr ≥ 98:2) depending on the geometry of starting material.[29] Later he also proposed the crotylation of ketones using BF_3•OEt_2 or montmorillonite clay as a catalyst.[30] Nakata used this reaction to form stereotriads as useful building blocks toward the syntheses of natural compounds (Scheme 5).[31]

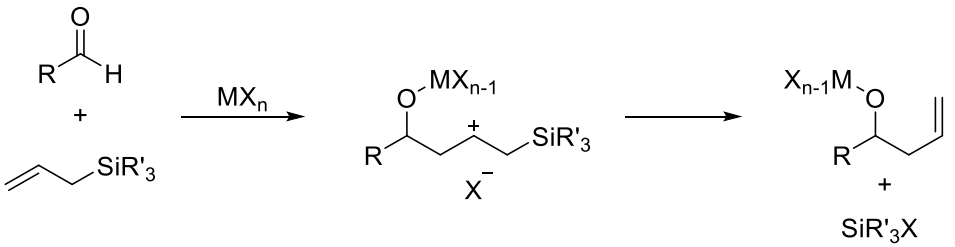


Scheme 5. Crotylation in aqueous media.

3.2.2 Enantioselective Catalytic Crotylation

Crotyl silanes and crotyl stannanes. Additions of crotyl silanes and crotyl stannanes to aldehydes are catalyzed by a LA, where the LA serves as an activating agent of the aldehyde toward the nucleophilic attack as well as to direct the addition.[6] The addition of allylic silanes has been described as a stepwise process (Scheme 6). Initial addition of an allylic silane to

activated aldehyde results in the formation of a carbocation that is stabilized by a carbon-silicon bond.[32] The subsequent cleavage of the silyl group provides the homoallylic product.

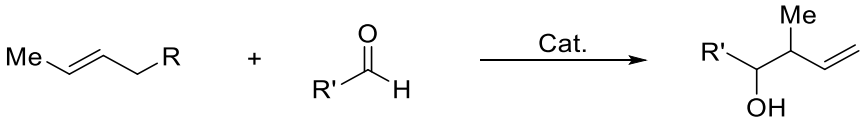


Scheme 6. Stepwise process of allylic silanes addition to aldehydes.

Marshall used modified Yamamoto's chiral acyloxy borane (CAB) catalyst **20** (Figure 3) for the catalytic reaction of crotyl stannanes (Table 2). He used 0.5 eq. of the catalyst **20** to promote the addition of the crotyl stannane to cyclohexyl carbaldehyde with 91% ee (Entry 1).[33] The application of BINOL **21** as a chiral moiety was used for the first time by Mikami.[34] He generated the catalyst *in sit*u by mixing (*S*)-BINOL **21** with $TiCl_2(O\text{-}i\text{-}Pr)_2$ in the presence of 4Å molecular sieves (Entries 2-3). BINOL/Ti(IV) system was also studied by Umani-Ronchi,[35] Keck[13], or Carreira[14,15] but not for crotylation.

In further evolution of this concept, Yamamoto developed silver/phosphine complexes. The *anti*/*syn* ratio of the products was found to be independent on the starting material geometry and the *anti*-products were formed predominantly. This is contradictory to the LA acid-catalyzed Type II reactions. However, no transmetalation has been observed and the mechanism pathway is still speculative. The addition of crotyl stannanes to benzaldehyde catalyzed by 20 mol% of BINAP/AgOTf complex gave *anti*-product (Entry 4)**.**[36] The BINAP/Ag catalytic system was also studied with crotyltrimethoxysilanes, also known as Sakurai-Hosomi[37] reaction. In this reaction, the transmetalation mechanism is proposed (Entry 5–6).[38] Further improvement has been achieved by using (*R*)-DIFLUOROPHOS **23** as a ligand in crotylation of ketones (Figure 3).[39]

Table 2. Addition of crotyl silanes or stannanes to aldehyde.



Entry	R	R'	Cat.	(mol%)	Yield (%)	*anti*/*syn*	ee (%)
1[a]	$SnBu_3$	C_6H_{11}	**20**	50	70	8/92	91
2	$SiMe_3$	$COOCH_3$	(*S*)-**21**/$TiCl_2$(O-*i*-Pr)$_2$	10	48	17/82	60
3	$SnBu_3$	$COOCH_3$	(*S*)-**21**/$TiCl_2$(O-*i*-Pr)$_2$	10	53	25/75	66
4	$SnBu_3$	Ph	(*S*)-**22**/AgOTf	20	56	85/15	94
5	$Si(OMe)_3$	Ph	(*S*)-**22**/AgF	6	77	92/8	96
6	$Si(OMe)_3$	Ph	(*S*)-**23**/AgF	5	60	90/10	96

[a]$(TFA)_2O$ (2.0 eq) and BH_3•THF(0.25 eq) was added to this reaction.

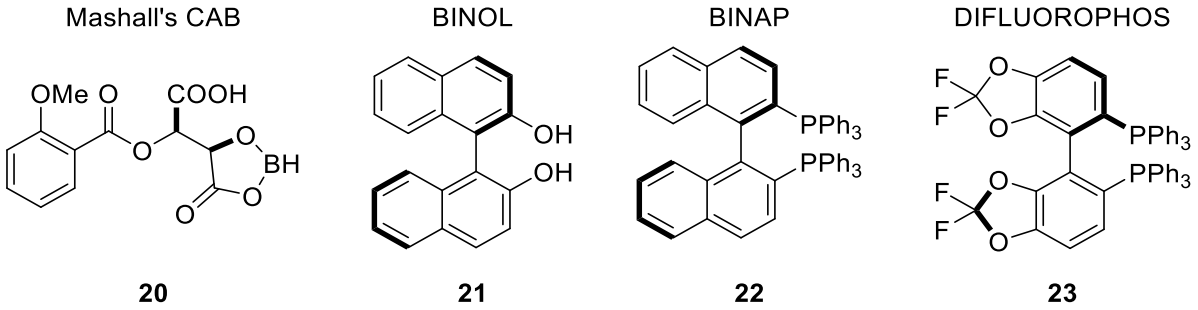
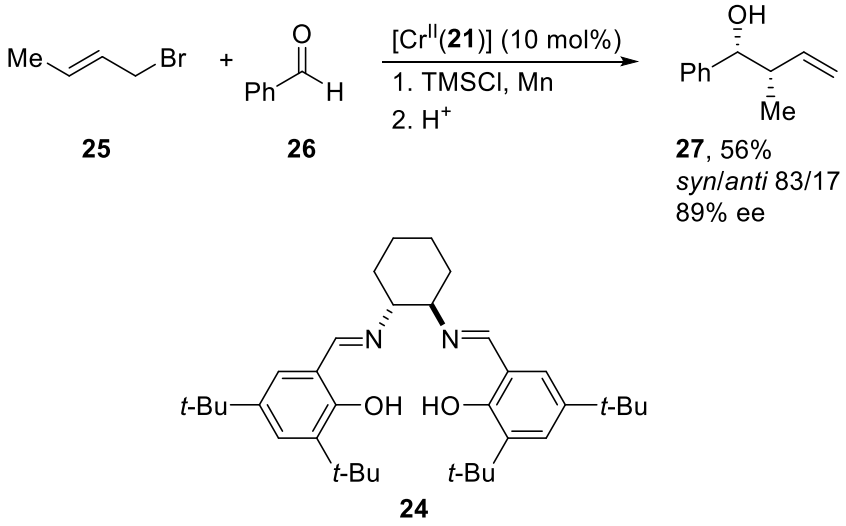


Figure 3. Chiral catalysts or ligands.

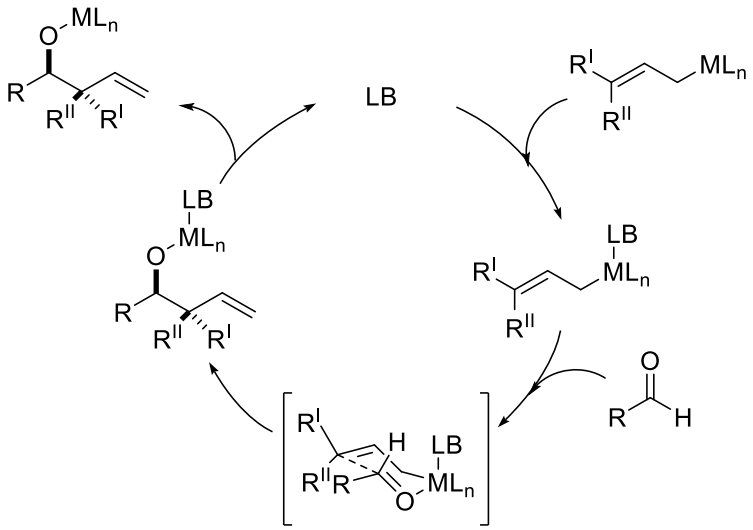
Grignard-type crotylation reagents. The addition of the Grignard-type reagents is known as a Nozaki-Hiyama or Nozaki-Hiyama-Kishi reaction.[40,41] Crotyl halides were firstly examined in a chromium-mediated addition to give preferentially the *anti*-product.[42] However, the first enantioselective Nozaki-Hiyama type crotylation was published by Umani-Ronchi using a chiral salen ligand **24** to induce the enantioselective course of the reaction. Surprisingly, when the salen ligand was added, the selectivity switched to the *syn*-product instead of the predicted *anti* (Scheme 7).[43]



Scheme 7. Crotylation with Grignard-type reagent.

Crotyltrichlorsilanes. Crotylation with a crotyltrichlorosilane or in general crotyltrihalosilanes proceeds through the Type I reaction mechanism. Due to the reduction of the s character on the Si atom together with the increase of its electrophilicity, the LB can coordinate to Si atom. The resulting complex of the crotyl reagent and the LB still reaches the

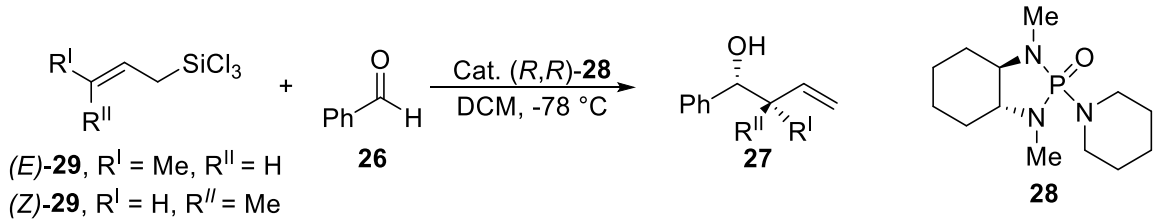
required acidity to coordinate to an aldehyde.[44] The reaction proceeds through the six-membered cycle and the transfer of the stereochemical information takes place. The catalytic cycle is terminated by the dissociation of the LB to re-enter the cycle (Scheme 8).[6]



Scheme 8. Lewis base catalyzed crotylation.

The use of anionic activators or strong donor solvents in the allylation has been first used by Sakurai[37] and Kobayashi.[45] The first enantioselective LB catalyzed crotylation was reported by Denmark in 1994 with a stoichiometric amount of the chiral phosphoramide **28** (Figure 4). He was able to get the *anti* or *syn* products based on the geometry of the crotyl reagent with 60–66% ee (Table 3).[46]

Table 3. Crotylation of benzaldehyde catalyzed by Denmark's chiral phosphoramide **28**.



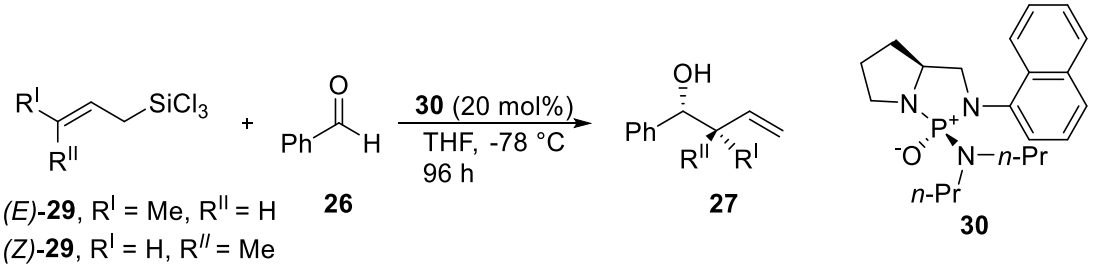
(E)-**29**, R^{I} = Me, R^{II} = H
(Z)-**29**, R^{I} = H, R^{II} = Me

26 **27** **28**

Entry	Silane	(*R*,*R*)-**28** (eq.)	Yield (%)	*anti*/*syn*	ee (%)
1	*(E)*-**29**	1.0	68	98/2	66
2	*(Z)*-**29**	1.0	72	2/98	60

Further improvement was done by Iseki who used a chiral phosphoramide derived from (*S*)-proline using **30** (Table 4).[47,48]

Table 4. Crotylation of benzaldehyde catalyzed by the Iseki's chiral phosphoramide **30**.



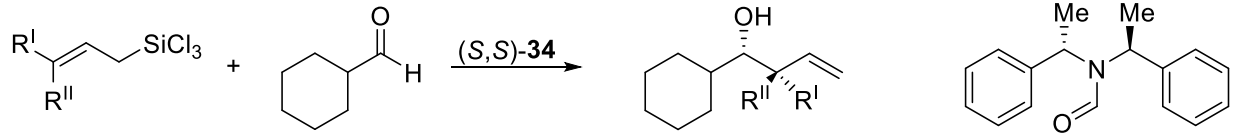
(E)-**29**, R^{I} = Me, R^{II} = H
(Z)-**29**, R^{I} = H, R^{II} = Me

26 **27** **30**

Entry	Silane	Yield (%)	*anti*/*syn*	ee (%)
1	*(E)*-**29**	90	2/98	83
2	*(Z)*-**29**	80	98/2	77

Based on Kobayashi's observation that dimethylformamide (DMF) as a solvent promotes the addition of trichlorosilane, Iseki developed a chiral DMF analog **34**. Although he tried to decrease the load of the catalyst, the allylation reaction did not proceed as expected. The yields and ee decreased due to a competitive pathway and *S*-enantiomer was formed instead of *R*-enantiomer (Table 5, Entry 1-2). To overcome this, the presence of hexamethyphosphoramide (HMPA) was found to be beneficial for the reaction rate and enantioselectivity (Entry 3-6).[49,50]

Table 5. Crotylation catalyzed by the Iseki's chiral formamide **34**.



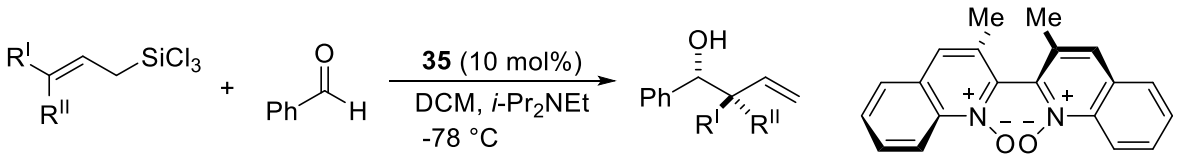
31, R^I = H, R^{II} = H
(E)-**29**, R^I = Me, R^{II} = H
(Z)-**29**, R^I = H, R^{II} = Me

32 **33** (*S*,*S*)-**34**

Entry	Silane	(*S*,*S*)-**34** (eq.)	HMPA (eq.)	Solvent	Time (days)	Yield (%)	*anti*/*syn*	ee (%)
1	**31**	1.0	-	DCM	7	81		68 (*R*)
2	**31**	0.1	-	DCM	7	12		32 (*S*)
3	**31**	0.25	1.0	DCM	7	33		94 (*R*)
4	**31**	0.2	1.0	C_2H_5CN	14	80		98 (*R*)
5	*(E)*-**29**	0.4	2.0	C_2H_5CN	21	92	>99/1	98 (*R*,*R*)
6	*(Z)*-**29**	0.4	2.0	C_2H_5CN	21	19	60/40	98 (*R*,*R*)

Further research showed that *N*-oxides and *N*,*N*′-dioxides represent a group of compounds that is capable of catalyzing the crotylation of aldehydes with silanes. The first catalytic enantioselective crotylation by *N*,*N*′-dioxide was published by Nakajima in 1998 (Table 6).[51] It was demonstrated that the presence of *i*-Pr$_2$NEt accelerated the course of the reaction. Later there has been ongoing development of new catalysts based on *N*-oxides and *N*,*N*′-dioxides. Only some of them, e.g. those published by Benaglia (**36**),[52] Zhu (**37**),[53] Hayashi (**38**),[54] Kočovský (**39**-**41**),[55,56] or Kotora (**42**)[57] have been used for catalysis of crotylation reaction (Figure 4).

Table 6. The first catalytic enantioselective crotylation using *N,N'*-dioxide **35**.



(*E*)-**29**, R^I = Me, R^{II} = H
(*Z*)-**29**, R^I = H, R^{II} = Me

26 **27** **35**

Entry	Silane	Yield (%)	*anti/syn*	ee (%)
2	*(E)*-**29**	68	97/3	86
3	*(Z)*-**29**	64	1/99	84

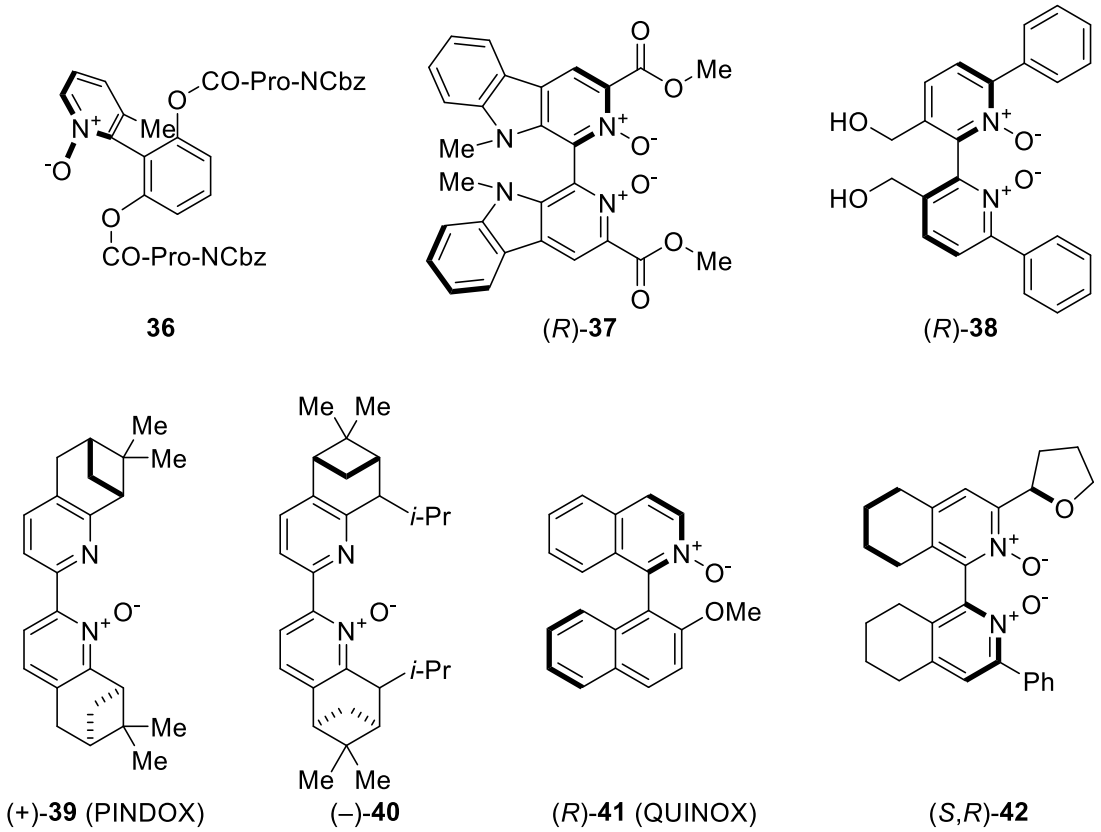
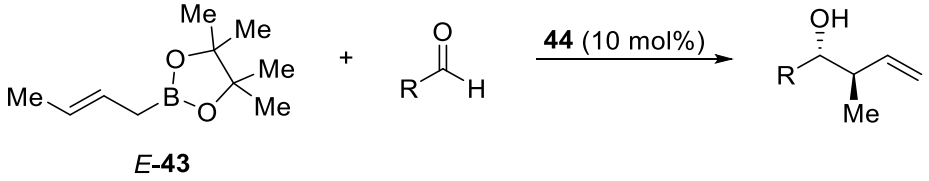


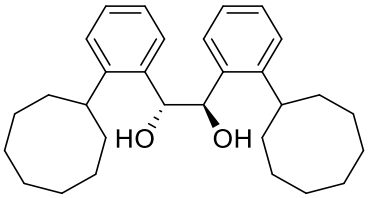
Figure 4. Chiral catalysts for crotylation using trichlorosilane.

Crotylboronic acid ester. The first example of catalytic enantioselective crotylboration was reported by Miyaura in 2002. He studied a LA system comprising (*S*)-BINOL **21** and a LA such as $AlCl_3$ or Et_2AlCl to enhance the catalytic enantioselective crotylation of benzaldehyde with the crotylboronate to obtain the respective homoallylic alcohol (Table 7, Entries 1 and 2).[58] Further research was done by Hall[59] who used Yamamoto's concept of Lewis acid-assisted Brønsted acid (LBA) catalyst.[60] In a LBA catalyst, the LA is coordinated to the BA to increase its acidity. The best results were obtained using a catalytic system consisting of Vivol **44** and $SnCl_4$. Vivol is required to be in a small excess to slow the dissociation of the diol•$SnCl_4$ complex and to suppress the competing racemic reaction catalyzed by free $SnCl_4$. The better enantioselectivity was obtained using (*E*)-crotylboronate to result in 95–96% ee (Entry 3-4).[59]

Table 7. Catalytic Crotylboration.



E-**43**

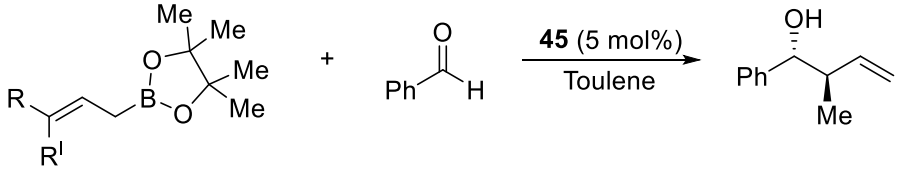


44 (*R*,*R*)-Vivol

Entry	R	Cat.	Yield (%)	ee (%)
1	Ph	(*S*)-**21**/$AlCl_3$	92	39
2	Ph	(*S*)-**21**/Et_2AlCl	40	51
3	$Ph(CH_2)_2CHO$	(*R*,*R*)-**44**•$SnCl_4$	93	96
4	$CH_3(CH_2)_3CHO$	(*R*,*R*)-**44**•$SnCl_4$	74	95

The previously mention catalytic systems for crotylboration have its limitation due to the presence of an undesirable metal, such as tin. However, Antilla has shown that chiral binaphthyl-derived phosphoric acids can be used to efficiently catalyze allyl- and crotylboration.[61] TRIP-PA **45** proved to be a very suitable catalyst for this type of reaction and allylation of various aldehydes was studied. In general, the allylation reactions proceeded with asymmetric induction (90-98% ee) with the exception of allylic aldehydes (73-79% ee). In addition, the TRIP-PA catalyzed crotylation of benzaldehyde was examined as well (Table 8).

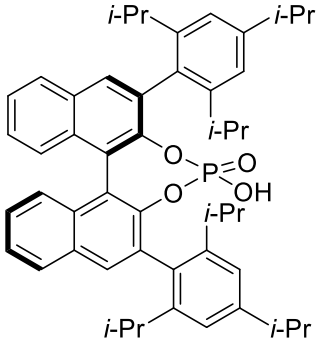
Table 8. Catalytic crotylboration with TRIP-PA **45.**



(*E*)-**43**, R = Me, R^I = H
(*Z*)-**43**, R = H, R^I = Me

26

27



45

Entry	**43**	T (°C)	*syn*/*anti*	Yield (%)	ee (%)
1	*E*	rt	2/98	96	96
2	*E*	0	2/98	96	99
3	*Z*	-30	98/2	95	94

Antilla also suggested that this type of reaction proceeds through the Type I[6] reaction mechanism involving a chair-like six-membered cyclic transition state. It is also suggested that the protonation of the boronate's **43** oxygen by phosphoric acid could be involved (Figure 5).

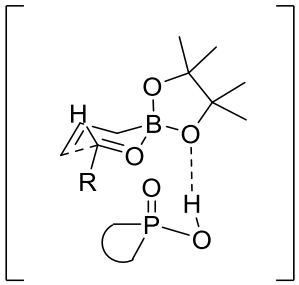
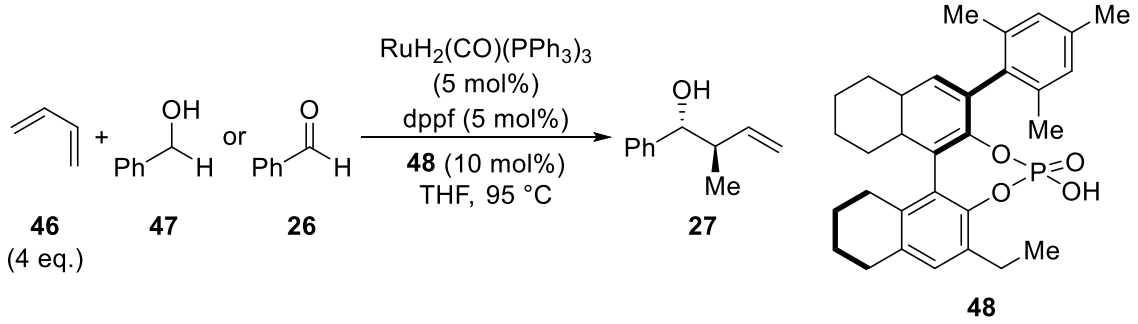


Figure 5. Suggested protonation of boronate by TRIP-PA **45**.

Krische crotylation. Krische developed catalytic crotylation reaction using butadiene **46** as the masked crotyl moiety in the presence of transition metal hydrides. The best results were obtained using $RuH_2(CO)(PPh_3)_3$ as a catalyst and BINOL-derived phosphoric acid as a chiral acid. Crotylation with butadiene proceeds also with alcohol with the same level of asymmetric induction (Table 9).[62,63] The course of the reaction is based on hydrometallation of butadiene that gives rise to a crotylmetal intermediate that is a reactive species. In addition, under the reaction conditions, alcohols are dehydrogenated to aldehydes, hence it is possible to use them as substitutes.

Table 9. Crotylation of aldehyde or alcohol with butadiene.



46 (4 eq.) **47** **26** **27** **48**

Entry	Oxidation level	Yield (%)	*anti*/*syn*	ee (%)
1	Alcohol	86	8/1	90
2	Aldehyde	74	8/1	88

3.3 Enantioselective Crotylation in Syntheses of Natural Compound

Crotylation has been used as a crucial step in the synthesis of many natural compounds. As the research of enantioselective crotylation continues, the trend is to use the catalytic procedures with achiral substrates instead of stoichiometric amounts of chiral reagents. Although Brown's crotylation is still the most frequently used method, recently have been reported total synthesis using different types of crotylation. The application of crotylation in syntheses natural compounds has been narrowed to selected examples published within the last 20 years. The part of the molecule that was constructed by enantioselective crotylation is highlighted: the blue part comes from an aldehyde and the red part from the crotyl reagent (Figure 6).

Dysoxylactam A **48** is a recently isolated macrocyclic lipid and is a potent multi-drug-resistant reverser. The key steps in the synthesis of dysoxylactam A **49** were Brown's crotylation and Krische's Ir-catalyzed allylation (green highlighted).[64]

Krische used double crotylation of diol as the crucial step in the synthesis of 6-deoxyerythronolide B **50**, the macrolide aglycone of antibiotic erythromycin A. (*S*)-Ir/SEGHOS **51** (2.5 mol%) was used as a catalyst giving the product with excellent enantioselectivity (≥99.9%) and good diastereoselectivity (dr = 6/1), but in a moderate yield (51%).[65]

The two enantioselective syntheses of natural compounds, (−)-elisabethadione **52** and (−)-erogorgiaene **53**, were reported by Malkov using *N*,*N*′-dioxide (−)-MAKDIOX **54** as a catalyst. Both compounds were found in a soft marine coral *Pseudopterogorgia elisabethae* and have a relatively simple structure with potential biological activity. Both crotylations proceeded with high yields (72-85%) and excellent enantioselectivity (97-98% ee).[66,67]

Last but not least example of catalytic enantioselective crotylation was done in our lab by Petr Koukal. He used TRIP-PA **45** (5 mol%) catalyst to synthesize (5*R*,6*S*)-(+)-pteroenone **55** with enantioselectivity >95% ee. Within this work, the crotylation reaction was also studied with *N*,*N*′-dioxide **42** (1.25-2.5 mol%) as a catalyst.[68]

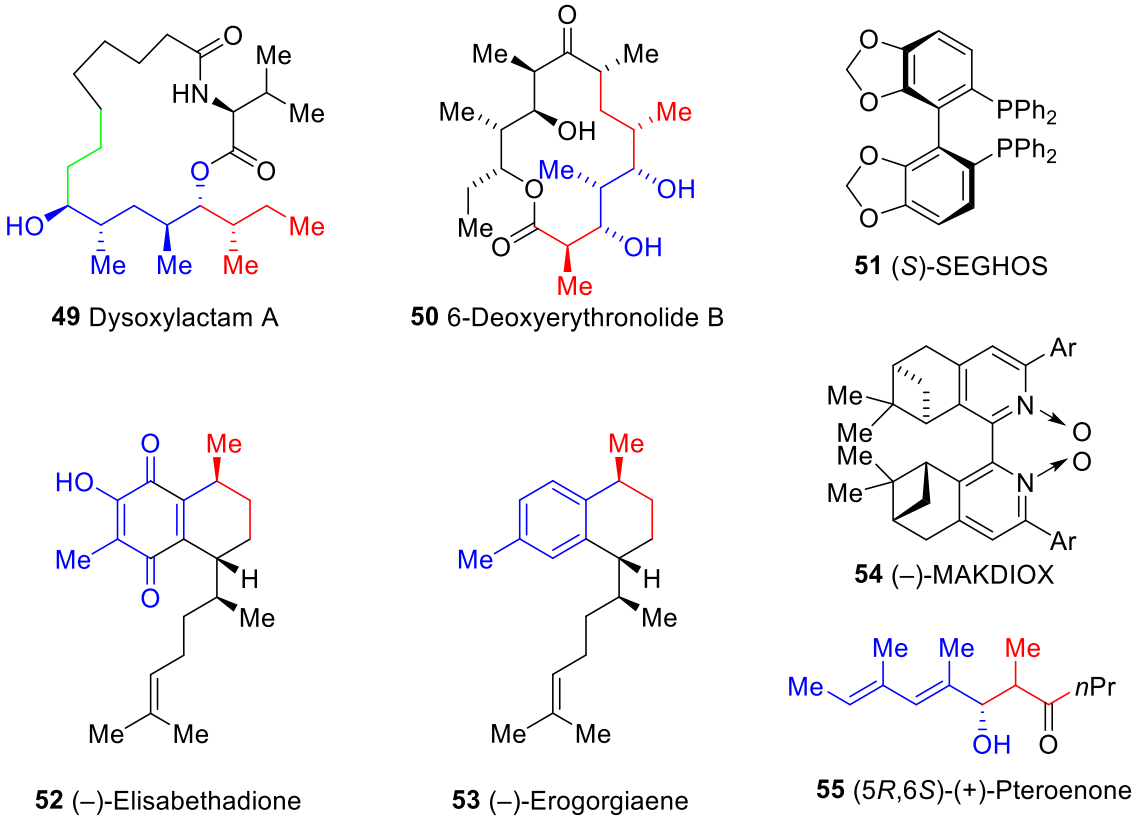


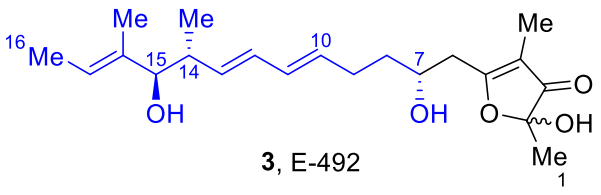
Figure 6. Syntheses of selected natural compounds by using various crotylation methods.

3.4 Natural Compounds Isolated from *Streptomyces* Genus

Actinobacteria that belong to the *Actinomyceteae* family and especially the genus *Streptomyces* is well known for its ability to produce diverse secondary metabolites that are bioactive compounds. They have been the most studied microorganism because their secondary metabolites often lead to the discovery of new therapeutic agents. Their antibacterial, antifungal, anticancer, antitumor, cytotoxic, cytostatic, anti-inflammatory, anti-parasitic, anti-malaria, antiviral, antioxidant, and anti-angiogenesis properties are very valuable in the pharmaceutical industry. *Streptomyces* produce over two-thirds of the clinically useful antibiotics of natural origin. In numbers around 23 000 antibiotics were discovered thanks to bacteria and roughly 10 000 were isolated from actinobacteria. Around 80% of actinobacteria are from the genus *Streptomyces*. There have been described over 500 *Streptomyces* bacteria and the microorganisms are usually isolated from soil or water.[69]

3.4.1 E-492

Alkenylfuranone E-492 **3** was first isolated from *Streptomyces* sp. Eco86 and indicated by Banskota. Their test for electron transport inhibitory activities was positive with IC_{50} values of 1.0 µg/ml against *Ascaris suum* NADH-fumarate reductase and 6.5 µg/ml against bovine heart NADH oxidase.[4] Lately, the same compound was isolated from *Streptomyces gramineus* derived from the lichen *Leptogium trichophorum* with six new actinofuranones D-I by the group of Li Han. They have tested them for anti-inflammatory activities because of their ability to inhibit nitric oxide (NO) production in LPS-stimulated RAW 264.7 macrophage cells. E-492 **3** attenuated the production of NO due to the suppression of the expression of nitric oxide synthase (iNOS) in LPS-induced RAW 264.7 cells in addition to this, E-492 **3** also inhibited LPS-induced release of proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α). These properties are valuable, therefore E-492 **3** can be potentially used as a model in the new drug development (Figure 7).[70]



3, E-492

Figure 7. Structure of natural compound E-492.

3.4.2 Actinofuranone A

Two polyketides actinofuranone A **2** (Figure 8) and actinofuranone B were first isolated from marine *Streptomyces* strain CNQ766 and identified by the Fenical group. Each of them showed weak *in vitro* cytotoxicity against mouse splenocyte T-cells and macrophages with IC_{50} values of 20 μg/mL.[3]

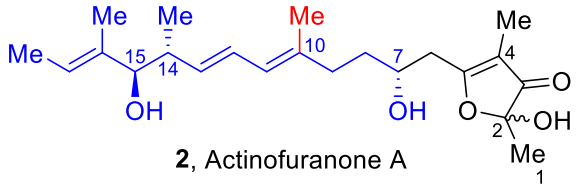


Figure 8. Structure of natural compound actinofuranone A.

3.4.3 JBIR-108

Exotoxin JBIR-108 **1** was first isolated from *Streptomyces gramineus* IR087Pi-4 by T. Doi's and K. Shin-ya's group as a white amorphous powder as a mixture of two diastereoisomers. They determined its structure and confirmed it by the total synthesis of both epimers in 2015. The compound has four centers of chirality (C1, C7, C14, and C15) and the epimers differed at C1. The epimers found in nature have the following absolute configuration: 1*S*, 7*R*, 14*R*, 15*R* and 1*R*, 7*R*, 14*R*, 15*R*.[2] Lately, it was found that the compound exists in nature in the form of 4 diastereoisomers differing in absolute configuration at C1 and C2.[70] The key steps of the published synthesis is Corey-Bakshi-Shibata reduction, vinylogous Mukaiyama aldol reaction, and Brown crotylation. JBIR-108 exhibits moderate cytotoxic activity against Meso-1, SKOV-3 and Jukart cells (IC_{50} values 2.5, 2.3 and 1.0 μM) that leads to cancer development of mesothelium, ovaria, and leukemia of T-lymphocytes (Figure 9).[2]

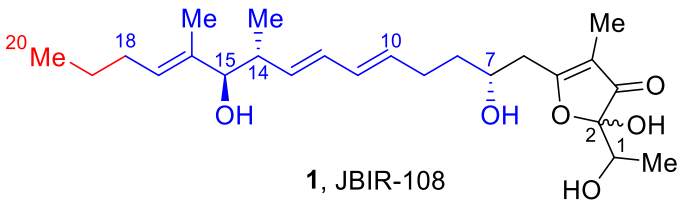
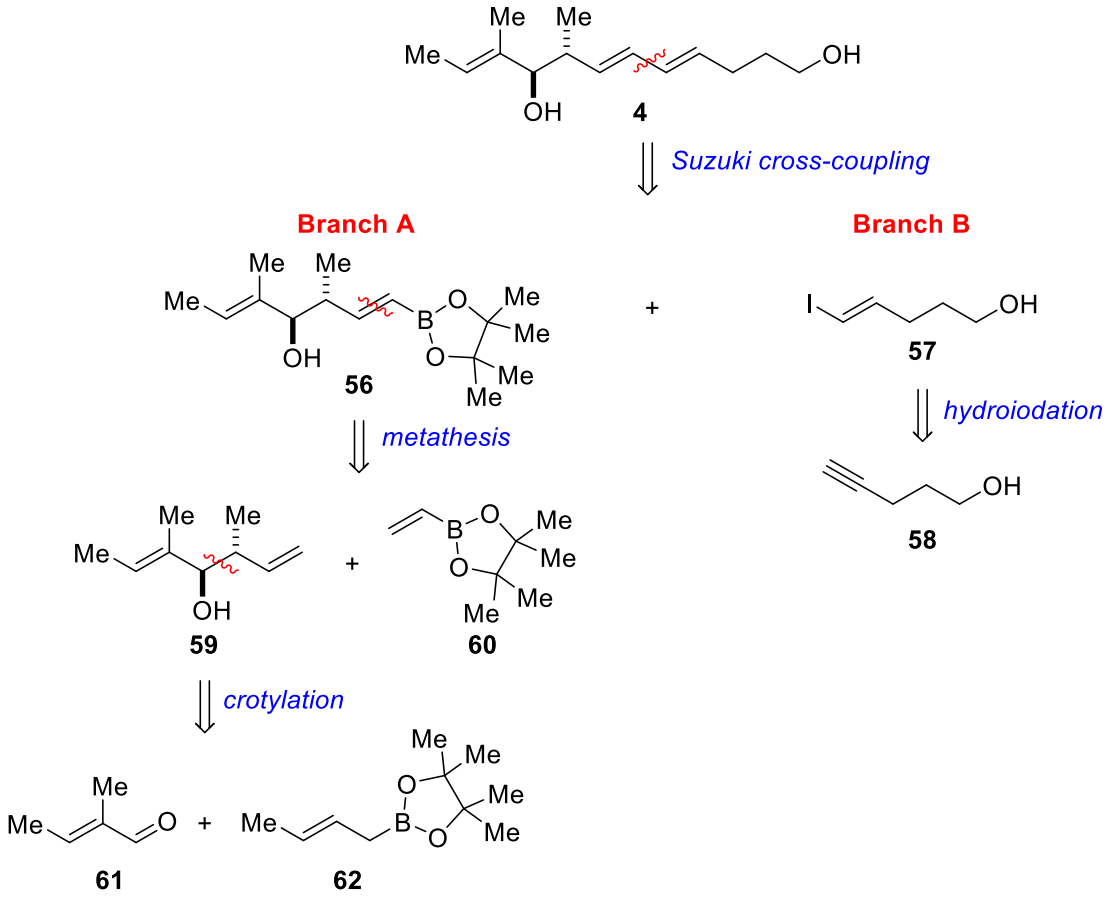


Figure 9. Structure of natural compound JBIR-108.

4 RESULTS AND DISCUSSION

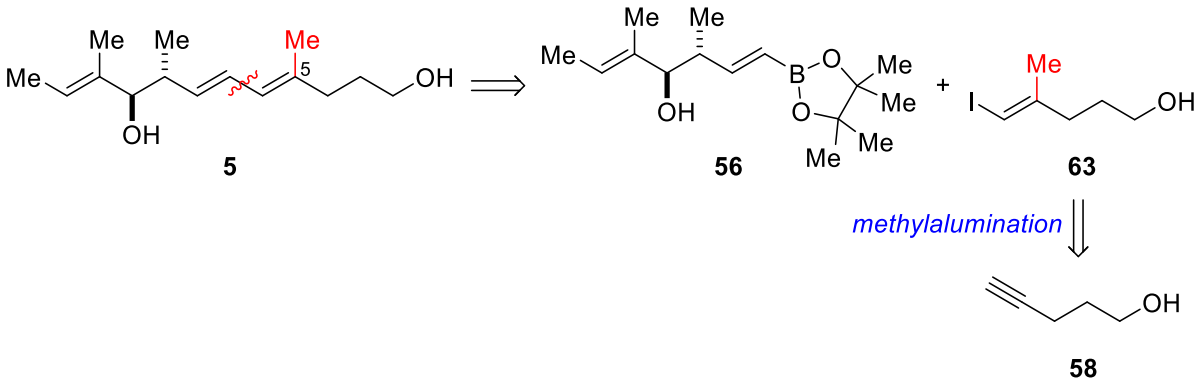
4.1 Retrosynthesis

Retrosynthetic analysis of the C7-C18 fragment of E-492. It was envisioned that the fragment **4** could be synthesized by Suzuki cross-coupling of two previously prepared fragments **56** (unsaturated acid pinacol ester) and **57** (iodoalkene) in branches **A** and **B**, respectively (Scheme 9). Iodoalkene **57** is expected to be prepared from pentynol **58** by hydroiodation (branch **B**). The synthesis of unsaturated pinacol ester of boronic acid **56** (branch **A**) is based on cross-metathesis of vinylboronic acid pinacol ester **60** and homoallylalcohol **59**. Homoallylalcohol **59** is envisioned to be prepared by enantioselective crotylboration of tiglic aldehyde **61** with crotylboronic acid pinacol ester **62**.



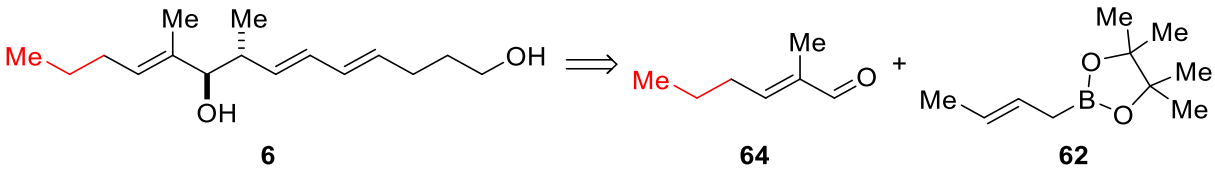
Scheme 9. Proposed retrosynthesis of the C7-C18 fragment of E-492.

Retrosynthetic analysis of the C7-C18 fragment of actinofuranone A. In actinofuranone A, there is an additional methyl group at carbon 5 in comparison with E-492, therefore the synthetic approach has to be modified by using vinyl iodide **63**. It is assumed that **63** is going to be prepared by methylalumination of pentynol **58** followed by iodonolysis. The synthetic route to the unsaturated acid pinacol ester **56** remains the same (Scheme 10).



Scheme 10. The retrosynthesis of the C7-C18 fragment of actinofuranone A.

Retrosynthetic analysis of the C7-C20 fragment of JBIR-108. As the JBIR-108 C7-C20 fragment **6** has its carbon sidechain extended by two methylene units, a different starting material is suggested for its synthesis. It is presumed that the first step of the synthesis will be crotylboration of aldehyde **64** (Scheme 11). The following steps remain to be the same as suggested in the retrosynthesis of C7-C18 fragment of E-492 **4** (Scheme 9).



Scheme 11. Starting material for the synthesis of the JBIR-108 C7-C18 fragment **6.**

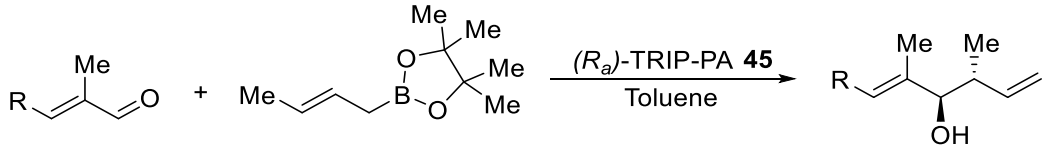
4.2 Catalytic Enantioselective Crotylboration

Previous studies of enantioselective crotylboration in our group indicated that the best results regarding both yield and enantioselectivity are achieved using TRIP-PA **45** as a catalyst,[71] hence it was the first choice to start the screening with. In addition, the results also showed that the use of (R_a)-TRIP-PA **45** leads to products possessing two newly formed centers of chirality with *R* configurations. All the three natural compounds, E-492, actinofuranone A and JBIR-108, have the same configuration.

First of all, the screening of crotylboration was done with tiglic aldehyde **61** catalyzed by **45** (5 mol%) on 0.2 mmol scale under different conditions (Table 10). The reaction was carried out for two days at -40 °C and it gave product **59** in a good yield (77%) and high enantioselectivity (96% ee) (Entry 1). However, as the TRIP-PA **45** catalyst is expensive, further studies with the reduced load of catalyst were done. The reduction of the catalyst's load to 2.5 mol% under the same temperature (−40 °C) led to a slightly higher yield (83%) but lower ee (89%) (Entry 2). An additional decrease of the enantioselectivity to 83% ee was observed when the reaction was executed at a higher temperature (−20 °C) (Entry 3). On the other hand, the same enantioselectivity of 96% was obtained at −60 °C (Entry 4) as in the case of the 5 mol% load (Entry 4), but the reaction time has to be extended to 7 days. Although the same concentration of reagents was maintained during the scale-up of the reaction to 1.2 mmol, the enantioselectivity dropped to 86% ee (Entry 5).

Then, the screening was focused on the crotylboration of aldehyde **64**. When the reaction was performed on a small scale (0.2 mmol) under the previously used condition (2.5 mol% load of catalyst, −60 °C) the enantioselectivity was only 88% ee even though the yield was still high (81 %) (Entry 6). To prevent the decrease of enantioselectivity during the scale-up, the load of aldehyde **64** was divided into five part and each part was added every 24 hours. Unfortunately, when the reaction was performed with 1.2 mmol load of the aldehyde, the enantioselectivity dropped even more to 82% (Entry 7). To improve the enantioselectivity, the load of the catalyst was increased to 5 mol% and homoallylalcohol was obtained with 88% ee (Entry 8).

Table 10. Screening of TRIP-PA catalyst in crotylboration of aldehydes **61** and **64**.



61: R = Me
64: R = Pr

62 (1.2 eq)

(3*R*, 4*R*)-**59**: R = Me
(3*R*, 4*R*)-**65**: R = Pr

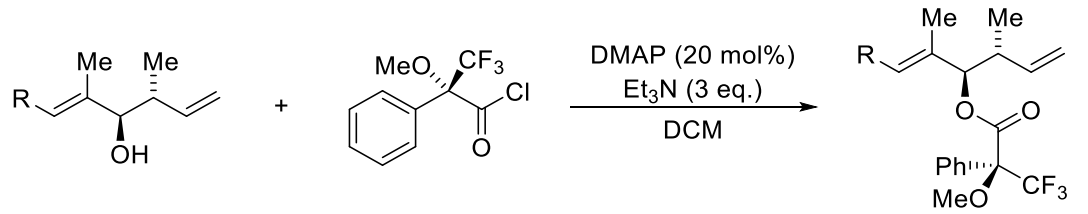
Entry	Aldehyde	(mmol)	(R_a)-TRIP-PA **45** (mol%)	t (days)	T (°C)	Yield (%)[a]	ee (%)[b]
1	**61**	0.2	5	2	−40	77	96
2	**61**	0.2	2.5	3	−40	75	89
3	**61**	0.2	2.5	3	−20	83	83
4	**61**	0.2	2.5	8	−60	70	96
5	**61**	1.2	2.5	7	−60	67	86
6	**64**	0.2	2.5	8	−60	81	88
7	**64**	1.2[c]	2.5	9	−60	83	82
8	**64**	1.2[c]	5	8	−60	86	88

[a] Isolated yields.

[b] Measured by Mosher ester derivatization followed by ^{19}F NMR.

[c] Dose of aldehyde was divided into 5 parts and each 24h in the first five days was added one.

The enantioselective excess was determined by converting homoallyl alcohols **59** and **64** to Mosher esters and by using ^{19}F NMR (Scheme 12). This approach was chosen because the unsaturated alcohol **59** is a volatile compound without absorption in the UV/visible light region so the use of HPLC with a chiral stationary phase using a UV detector wasn't feasible. Another possibility to overcome this problem was to protect the hydroxy group with *tert*-butyldiphenylsilyl (TBDPS) group to make the compound absorb in UV and to use HPLC analysis, but it did not work either. Unfortunately, efforts to find a suitable stationary phase able to separate both enantiomers were not met with success. In conclusion, the derivatization with Mosher chloride followed by ^{19}F NMR (Scheme 12) was found to be the most suitable solution to determine the enantiomeric ratio.



(3*R*, 4*R*)-**59**: R = Me
(3*R*, 4*R*)-**65**: R = Pr

66, 1.2 eq

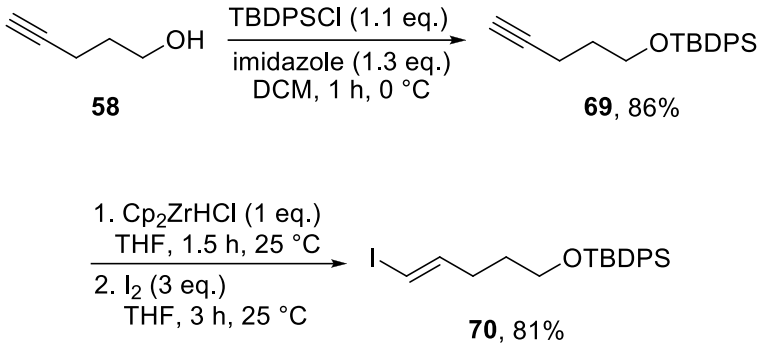
(3*R*, 4*R*)-**67**: R = Me
(3*R*, 4*R*)-**68**: R = Pr

Scheme 12. Mosher chloride derivatization.

4.3 Synthesis of C7-C18 Fragment of E-492

Synthesis of the racemate (BSc's thesis results). My bachelor's thesis concerned a study toward a racemic synthesis of the C7-C18 fragment of E-492 **4**. Since the enantioselective synthesis from the racemic one differs in the crotylboration step of the synthesis, the most of synthetic endeavors follow the previously developed methods and procedures, but they were carried out with enantioenriched substances. The only reactions that have not been carried out within the framework of my MSc's study are those that lead to the preparation of compounds in the branch **B** (Scheme 9).

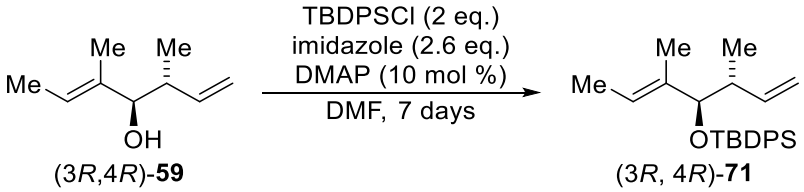
In order to proceed with the synthesis toward the C7-C18 fragment of E-492 **4**, I focused on the preparation of substrates in the branch **B** (Scheme 13). At the outset was prepared the protected alcohol **69** by the reaction of alcohol **58** with TBDPSCl in 86% yield. Then its hydrozirconation with the Schwartz reagent followed by iodonolysis provided vinyl iodide **70** in 81% yield.



Scheme 13. Synthesis of Branch **B**.

Enantioselective synthesis. To continue the synthesis of fragment **4** the previously prepared homoallylic (3*R*,4*R*)-**59** alcohol with 86% ee was protected with the TBDPS group (Table 11), the same group was used for the protection of the hydroxy group in Branch **B.** The reason to use the same protecting group was that both hydroxy groups can be deprotected under the same reaction conditions in the last step of the synthesis. The protection of the secondary hydroxy group proceeded with modest yields, presumably because of steric hindrance. The isolated yield of **71** was only 52% after 7 days (Entry 1); however, increasing the reaction temperature to 80 °C resulted in its 71% yield also after 7 days (Entry 2).

Table 11. Protection of the secondary hydroxy group.

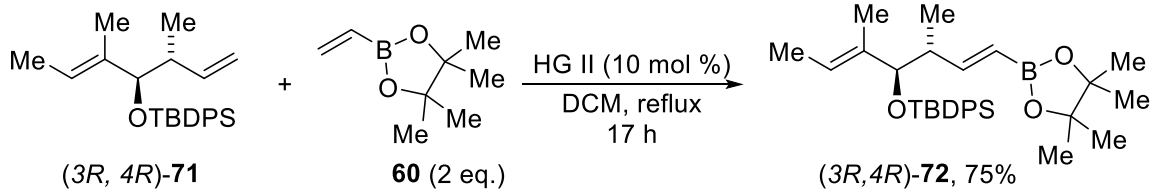


Entry	T (°C)	Yield (%)[a]
1[b]	25	52
2	80	71

[a] Isolated yields.

[b] BSc's thesis result.

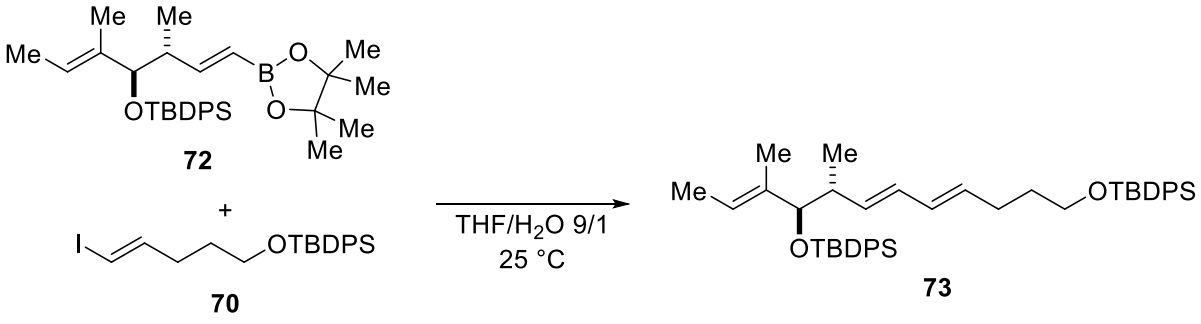
In the rest of the synthesis were used the same reaction conditions and methods as in the bachelors' thesis. The cross-metathesis between the protected homoallylic alcohol (3*R*,4*R*)-**71** with vinylboronic acid pinacol ester **60** was catalyzed by Hoveyda-Grubbs 2nd generation catalyst (HG II) and it furnished a new vinyl boronic acid derivative (3*R*,4*R*)-**72** in a nice 75% yield (Scheme 14. Cross-metathesis of protected homoallylic alcohol (3R,4R)-71..



Scheme 14. Cross-metathesis of protected homoallylic alcohol (3*R*,4*R*)-**71**.

In the next step was carried out Suzuki cross-coupling to link the unsaturated pinacol ester of boronic acid (3*R*,4*R*)-**72** and the vinyl iodide **70**. The cross-coupling was attempted under different conditions to ensure the highest possible yield of (3*R*,4*R*)-**73** (Table 12). When the PEPPSI catalyst and Cs_2CO_3 were used as a base the reaction did not take place and no product was formed (Entry 1). On the other hand, the use of a combination of $Pd(PPh_3)_4$ with NaOH yielded the desired product (3*R*,4*R*)-**73** in a reasonable 50% yield (Entry 2). Gratifyingly, by using the same Pd-catalysts and TlOEt was obtained (3*R*,4*R*)-**73** in a good 58% yield (Entry 3). This result is in accordance with the previously made observation by Roush[73] that TlOEt is a base of choice for the formation of diene by coupling of vinyl boronic acids and vinyl iodides under Suzuki conditions.

Table 12. Screening of condition of Suzuki cross-coupling.

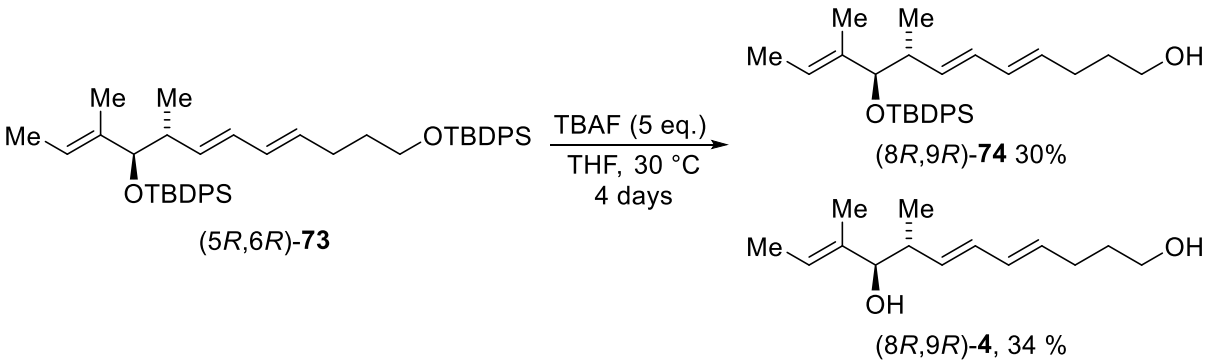


Entry	Catalyst	mol%	Base	eq.	T (°C)	Yield (%)[a,b]
1	PEPPSI	10	Cs_2CO_3	2.2	50	-
2	$Pd(PPh_3)_4$	10	NaOH	2.2	25	50
3	$Pd(PPh_3)_4$	5	TlOEt	3	25	58

[a] Isolated yields.

[b] BSc's thesis result.

Deprotection of the hydroxy groups was done using tetra-*n*-butylammonium fluoride (TBAF) in THF. The deprotection proceeded in two stages: first reacted the sterically less hindered primary alcohol moiety, then the deprotection of the secondary one took place. The deprotection of the more sterically hindered alcohol moiety was very sluggish. It could be accelerated by increasing the load of TBAF, but the more basic conditions led to the elimination of the secondary hydroxy group toward the fully conjugated system. The same phenomenon was observed by Petr Koukal with similar substrates.[71] In view of the aforementioned, the reaction was not run to completion and the fully deprotected product compound (8*R*,9*R*)-**4** was separated from the monoprotected (8*R*,9*R*)-**74**, which was recycled and again subjected to deprotection. In this manner, I was able to secure the desired product (8*R*,9*R*)-**74** in the overall 34% yield[I] (Scheme 15). The overall yield was also reduced due to repeated purification (two column chromatographies and one preparative TLC). In addition, the product **4** (all *trans* isomer) contained small amount of impurities, which are presumed to be *cis,trans* isomers. Judging from the ^{1}H NMR spectrum there are two side products (Figure 10). The major one is predicted to be *cis* at carbon 8. The coupling constant (*J*) of the main product **4** at carbon 9 at 5.65 ppm (dt, *J* = 14.4, 7.0, Hz) refers to *trans* coupling constant and the same signal for the major impurity refers to *cis* at 5.38 ppm (dt, *J* = 10.4, 7.5, Hz). The overall purity of the main product **4** was calculated to be 86%.



Scheme 15. Deprotection of the hydroxy groups.

[I] The measurement of final enantiopurity is in the process.

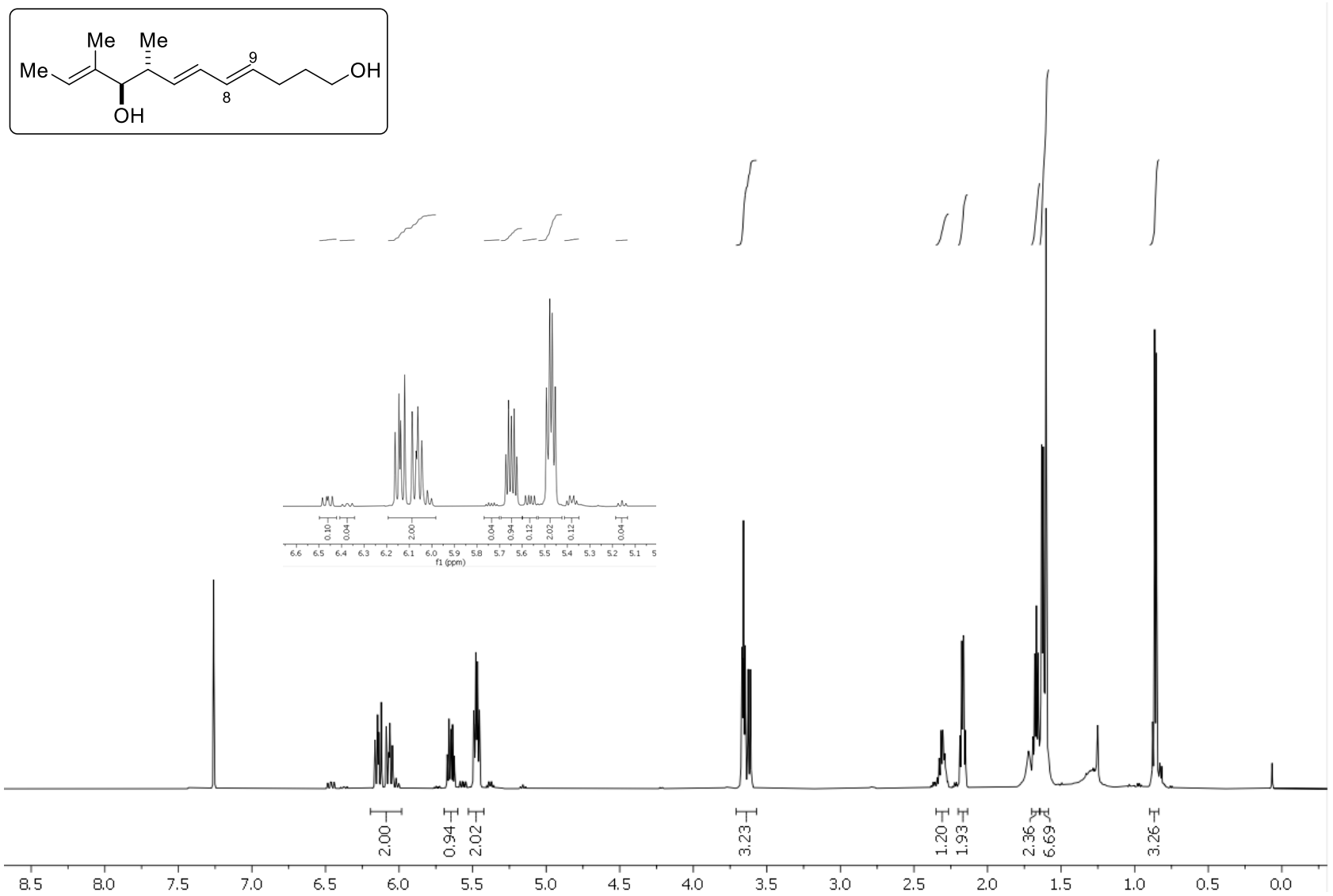
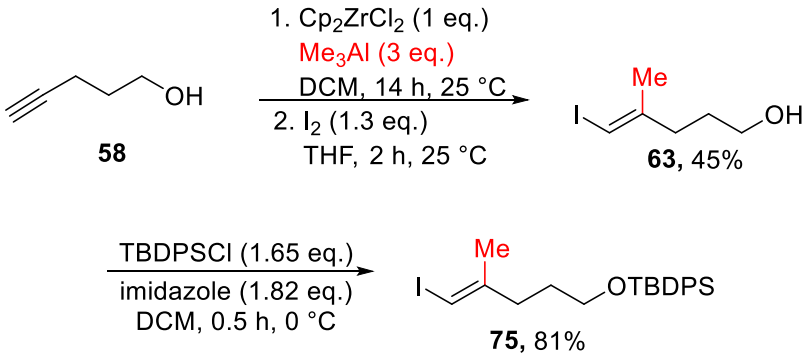


Figure 10. ^{1}H NMR spectrum of desired product **4**.

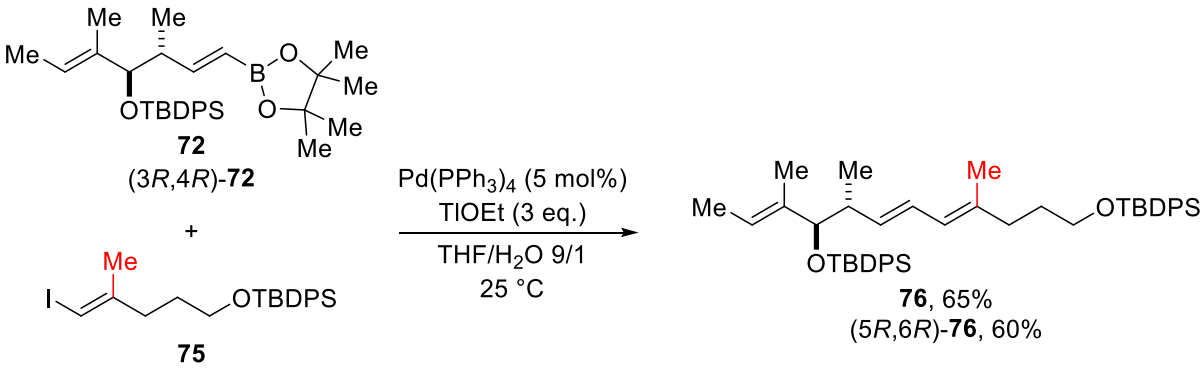
4.4 Synthesis of C7-C18 Fragment of Actinofuranone A

Synthesis of iodide 63. The synthesis of iodide for Suzuki cross-coupling had to be changed. Instead of hydroiodation, the methylalumination of pentynol **58** followed by iodonolysis was used. There were a couple of published procedures for methylalumination of hex-5-yn-1-ol giving overall yields 80-98%,[74] but unfortunately, after a few experiments, my best results of methylalumination of pent-4-yn-1-ol did not provide **63** in more than 45% yield (Scheme 16). I assume that the low yields were caused by the presence of protic impurities diminishing the yield of the reaction (the methylalumination reaction is sensitive to protic substances). Prior to the best attempt, the starting compounds were meticulously purified, pent-4-yn-1-ol was distilled, iodine was purified by sublimation and the Cp_2ZrCl_2 was dried under the vacuum at 50 °C. After the methylalumination/iodonolysis step, the hydroxyl group in **63** was protected with the TBDPS protecting group giving **75** in a good 81% yield.



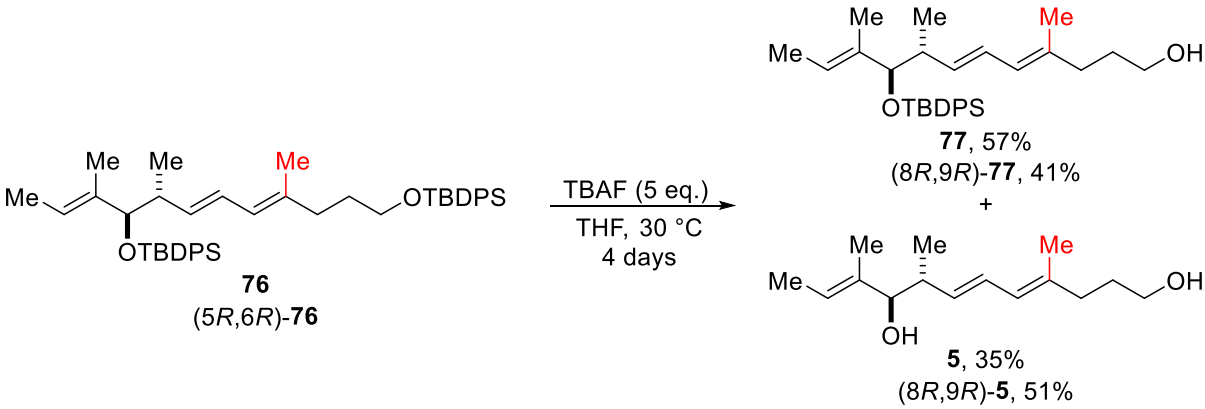
Scheme 16. Synthesis of iodide with protected hydroxy group **75**.

The last steps toward the actinofuranone A fragment 5. Iodide **75** was used in the next step of the synthesis, where it was coupled by Suzuki cross-coupling with the unsaturated pinacol ester of boronic acid **72**, respectively (3*R*,4*R*)-**72** (starting from homoallylic alcohol with 86% ee). Both syntheses, the synthesis of racemate **76** and the synthesis of (5*R*,6*R*)-**76** was achieved under the same condition using $Pd(PPh_3)_4$ as a catalyst and TlOEt as a base. The yields of this reaction were good (65% for racemate **76** and 60% for enantioenriched (5*R*,6*R*)-**76**) and comparable (Scheme 17).



Scheme 17. Suzuki cross-coupling.

Deprotection of the hydroxy groups using TBAF (5 eq.) led to the formation of a mixture of monodeprotected and fully deprotected compounds (Scheme 18). Even though the same conditions were used the yields were different. The deprotection of racemate **76** gave 57% yield of compound **77** and 35% yield of the desired product **5**. On the other hand, the deprotection of the enantioenriched (8*R*,9*R*)-**76** gave (8*R*,9*R*)-**77** in 41% yield and the desired product (4*R*,5*R*)-**5** in 51% yield and 86% ee, therefore the final enantiopurity did not change through the syntheses. In the ^{1}H NMR spectra of **5** or (8*R*,9*R*)-**5**, the double bond isomers were not observed.

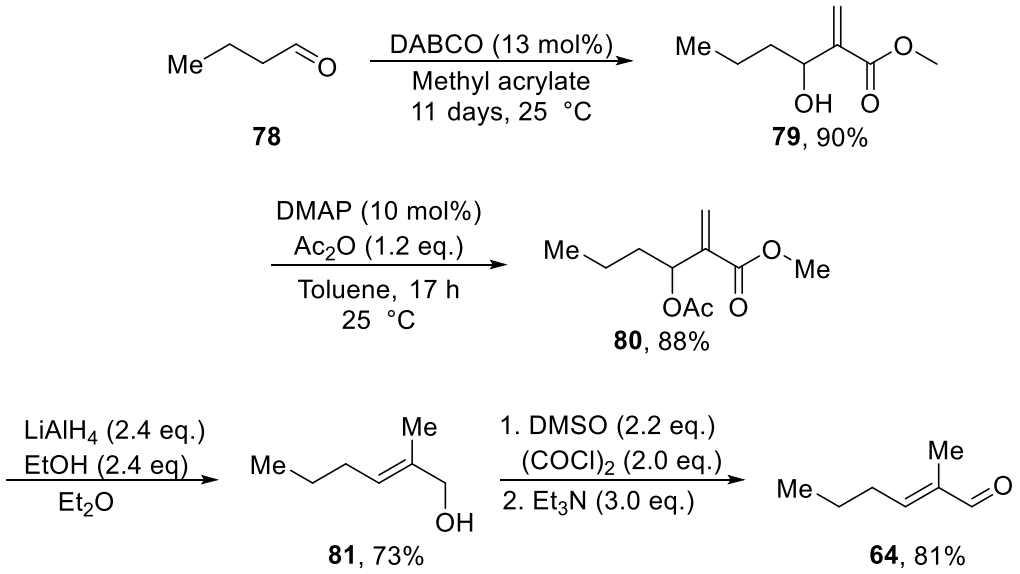


Scheme 18. Deprotection of the hydroxy groups.

4.5 Synthesis of C7-C18 Fragment of JBIR-108

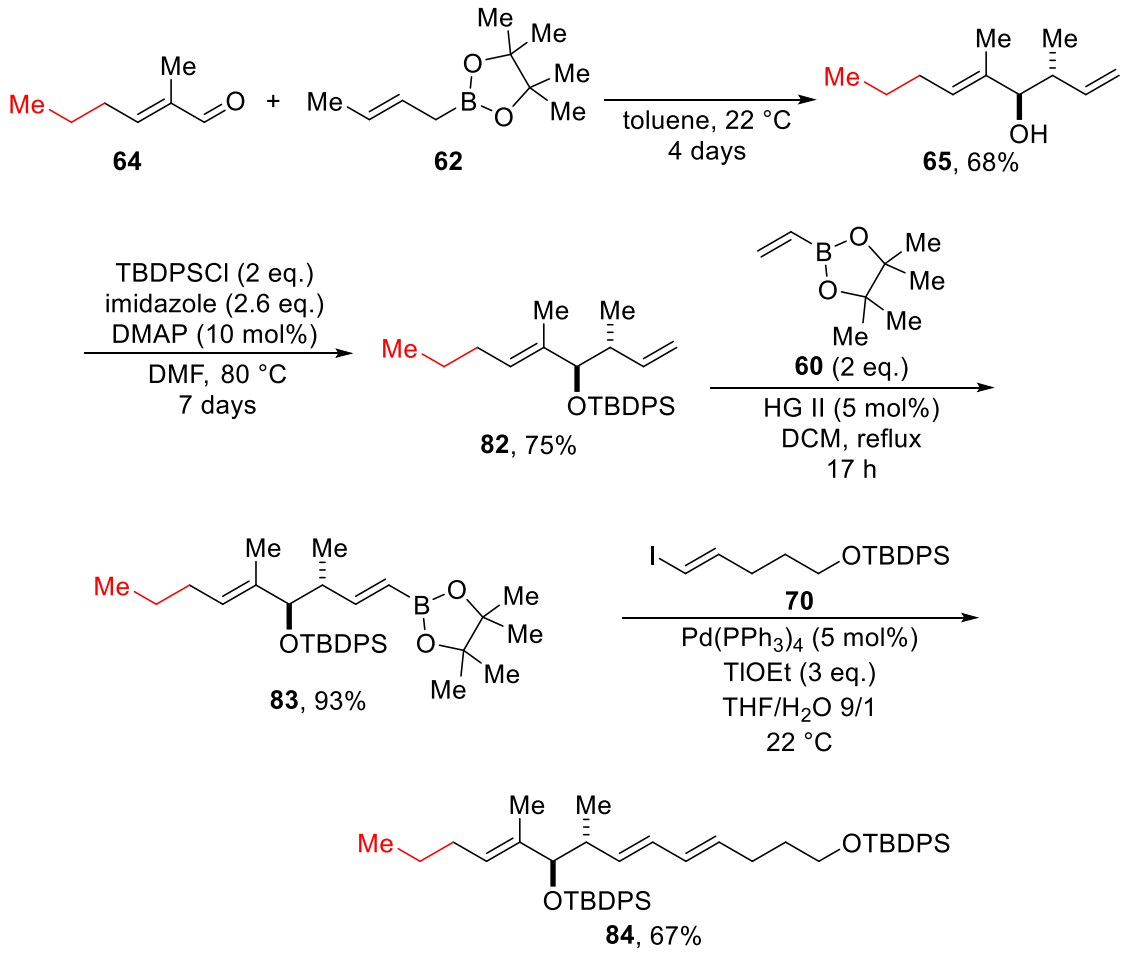
Synthesis of the starting material. The starting material for the crotylboration, aldehyde **64**, was prepared in four steps synthesis (Scheme 19). Firstly, the Baylis-Hillman reaction was performed with butanal and methyl acrylate using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a catalyst. The reaction gave **79** in the excellent yield (90%). In the next step, the hydroxy group was acetylated with a satisfying yield of 88%. After that, the reduction with $LiAlH_4$

gave an unsaturated alcohol **81** in 73% yield. Then **81** was oxidized by Swern oxidation to the aldehyde **64** in a high yield of 81%.



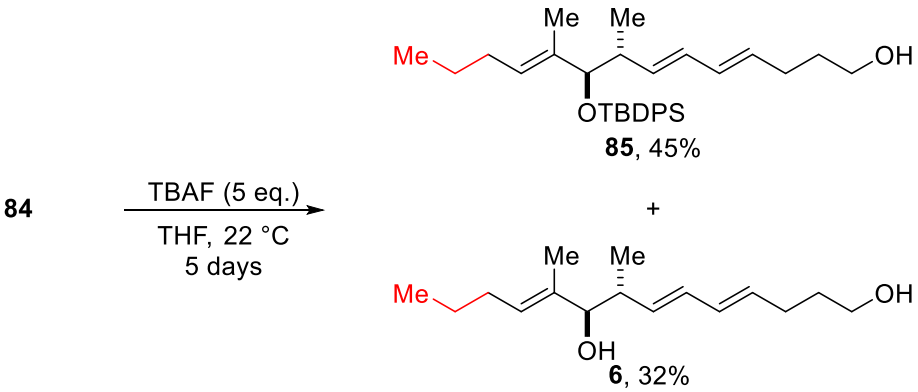
Scheme 19. Preparation of aldehyde **64**.

Further steps toward the racemic synthesis of fragment C7-C20 of JBIR-108. The starting aldehyde **64** was used in the crotylboration with crotylboronic acid pinacol ester **62** without the use of a chiral catalyst to yield the racemic homoallylic alcohol **65** in 68% (Scheme 20). In the next step, it was protected with the TBDPS group to give **82** with a reasonable yield of 75%. Then it was used in the cross-metathesis reaction with vinylboronic acid pinacol ester **60** catalyzed by HG II catalyst. The reaction gave **83** in the excellent 93% yield. Then the previously prepared unsaturated pinacol ester of boronic acid **83** and vinyl iodide **70** were joined together by Suzuki cross-coupling using TlOEt as a base and $Pd(PPh_3)_3$ as a catalyst to yield **84** in 67%.



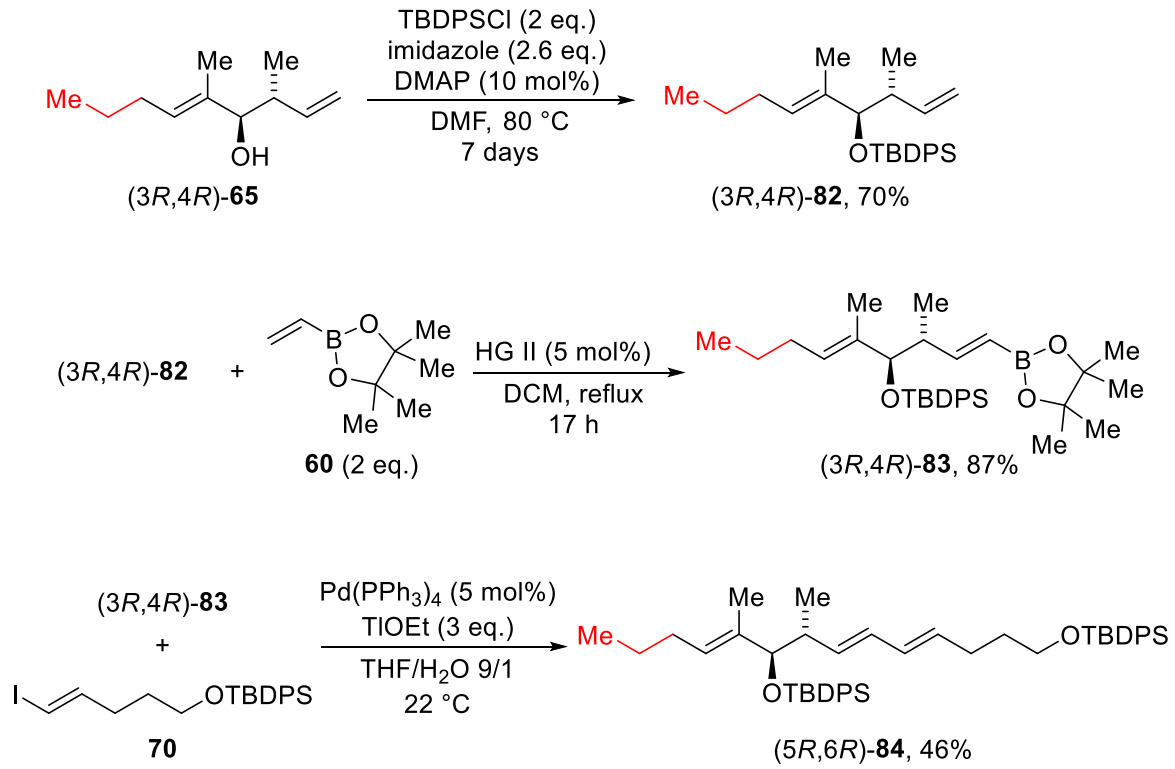
Scheme 20. Further steps toward the synthesis of fragment C7-C20 of JBIR-108.

The deprotection of the hydroxy groups was carried out using five equivalents of TBAF (Scheme 21). After five days, the reaction was quenched and gave a mixture of the partially deprotected product **85** (45% yield) and the fully deprotected desired product **6** (32% yield). Unfortunately, there were also visible the impurities caused by *cis-trans* isomerization in the ^{1}H NMR spectrum similar to those observed in the spectrum of the C7-18 fragment of E-492 **4**.



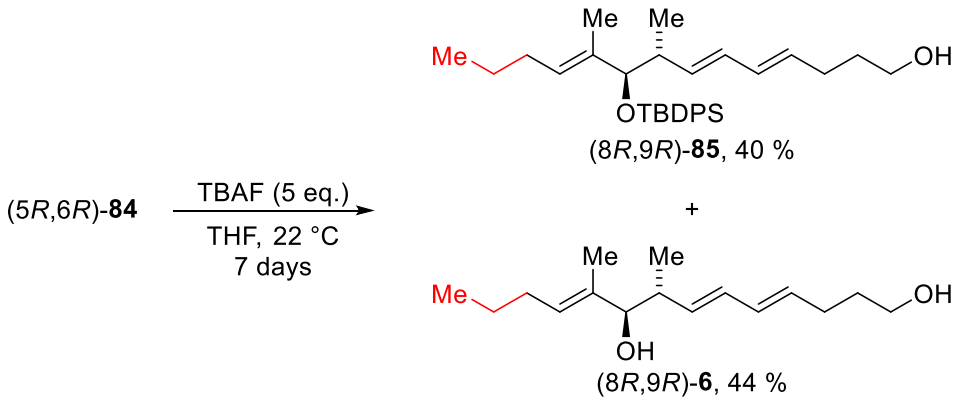
Scheme 21. Deprotection of the hydroxy groups.

Further steps toward the enantioselective synthesis of fragment C7-C20 of JBIR-108. The enantioselective synthesis of the desired product (8*R*,9*R*)-**6** was achieved under a similar condition as the synthesis of racemate **6** except the crotylboration step. The crotylboration of aldehyde **64** was done under the catalytic condition with (R_a)-TRIP-PA catalyst (5 mol%) and this step was already discussed in detail in chapter 4.2. The homoallylic alcohol (3*R*,4*R*)-**65** with 85% ee was protected with the TBDPS group and furnished (3*R*,4*R*)-**82** in 70% yield (Scheme 22). The cross-metathesis in the next step of the synthesis gave compound (3*R*,4*R*)-**83** in the excellent 87% yield. The Suzuki cross-coupling of unsaturated acid pinacol ester (3*R*,4*R*)-**83** and iodide **70** gave the final product with protected hydroxy groups (5*R*,6*R*)-**84** in 46% yield.



Scheme 22. Further steps toward the enantioselective synthesis of fragment C7-C20 of JBIR-108.

The reaction time was extended to seven days to shift the equilibrium in the deprotection reaction toward the fully deprotected product (8*R*,9*R*)-**6**, (Scheme 23). This led to 44% yield of the desired product (8*R*,9*R*)-**6** and 40% yield[II] of (8*R*,9*R*)-**85**.



Scheme 23. The deprotection of hydroxy groups.

[II] The measurement of final enantiopurity is in the process.

5 EXPERIMENTAL PART

5.1 General

Reactions that are sensitive to oxygen or air moisture were carried out under the argon atmosphere in dry solvents. Flask and reaction vessels, in which the reaction were carried out, were dried using a heat-gun under reduced pressure. All the commercially available chemicals were purchased from available sources (Sigma Aldrich, Acros Organics, Alfa Aesar, Strem Chemicals, and PENTA) and were used without further purification unless noted. Solvents were purified and dried by distillation from natrium/benzophenone (THF, Et_2O, toluene), calcium hydride (dichloromethane) or by molecular sieves (DMF, EtOH). Other solvents used for column chromatography were previously distilled. Sonication while bubbling of argon through the solvent was used for their degassing.

All reactions were monitored using TLC on Merck TLC silica gel 60 F_{254}. Compounds were visualized by UV lamp (254 nm) or using $KMnO_4$ stain (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH, 200 mL H_2O) or the anisaldehyde stain (15 g anisaldehyde, 2.5 mL conc. H_2SO_4, 250 mL EtOH), followed by gun heating. For column chromatography, the silica gel 60 (0,040–0,063 mm, MERCK) was used.

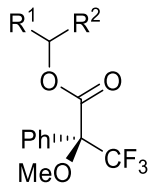
NMR spectra were measured by NMR Spectrometer Bruker Avance III (400MHz) (400.13 MHz for ^1H, 100.61 MHz for ^{13}C, and 376.50 MHz for ^{19}F) or on Bruker Avance III (600 MHz) (600.17 MHz for ^1H and 150.04 for ^{13}C). Measurements were carried out at 25 °C. Chemical shifts are given in δ scale listed in ppm. All the NMR spectra were referenced to a residual solvent signal of $CDCl_3$ (^1H δ 7.26, ^{13}C δ 77.16). Obtained spectra were processed by MestReNova program.

Infrared spectra were measured in KBr pellets or by Hermo Nicolet AVATAR 370 FT-IR spectrometer and reported in wave numbers (cm^{-1}). Mass spectra were recorded on VG-Analytical ZAB SEQ spectrometer. Automatic polarimeter Autopol III was used for optical rotation measurement and the results are given in $deg \cdot mL \cdot g^{-1} \cdot dm^{-1}$ with accuracy ±2 and the mass concentrations in g/100 mL. Enantiomeric excess was measured by Mosher ester analysis or by HPLC analysis measured on Shimadzu chromatograph with Daicel Chiralpak® columns. IR and HRMS measurements of some products are not included within this work as the results of the analysis haven't been received or measured before the submission of the thesis.

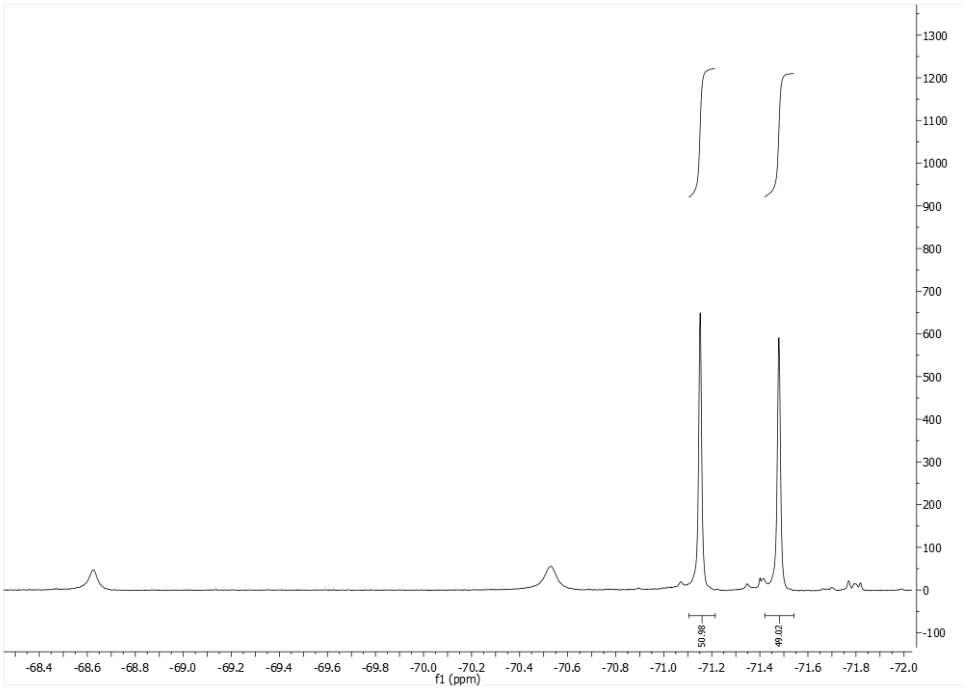
5.2 Screening of enantioselective crotylboration of various aldehydes

The catalyst load, reaction temperature, and reaction time are variable conditions and there are listed together with ee and yield of the certain reaction in Table 10. In a dry Schlenk flask was dissolved (R_a)-TRIP-PA **45** and tyglic aldehyde (0.2 mmol) in dry toluene (2 mL). After cooling down the solution to temperature as given in the Table 10, (*E*)-crotylboronic acid pinacol ester **62** (52 µL, 0.24 mmol) was added. Then the reaction mixture was stirred at the same temperature. It was quenched by DIBAL-H (1M solution in toluene, 0.2 mL) and the reaction mixture was stirred for 30 minutes. Then HCl (1M solution, 0.2 mL) was added and the reaction mixture was warmed up to 22 °C. The aqueous phase was separated and extracted with pentane (2×10 mL), the combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of pentane → 20/1 pentane/Et_2O) yielded the title compound as a colorless oil.

Synthesis of Mosher esters



To a 4 mL vial DMAP (1 mg, 0.01 mmol), dichloromethane (1 mL), (*R*)-MTPA-Cl (12 µL, 0.07 mmol) and the corresponding alcohol (0.06 mmol) were added followed by the addition of Et_3N (24 µL, 0.18 mmol). The resulting yellow solution was allowed to react overnight. The resulting mixture was concentrated under reduced pressure to give corresponding (*S*)-MTPA-X Mosher esters as yellow crystals and ^{19}F NMR spectra of crude product were recorded.


1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
50.98
49.02
-68.4
-68.6
-68.8
-69.0
-69.2
-69.4
-69.6
-69.8
-70.0
-70.2
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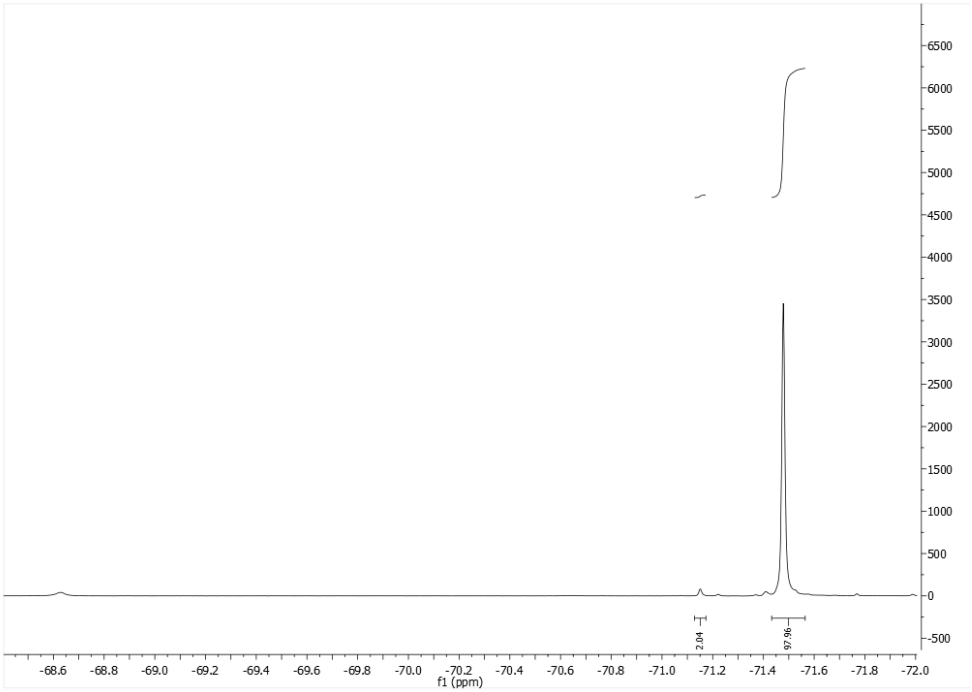
-70.6
-70.8
-71.0
-71.2
-71.4
-71.6
-71.8
-72.0
f1 (ppm)


6500
6000
5500
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4500
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2000
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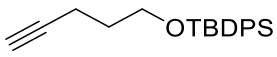
1000
500
0
-500
2.04
97.96
-68.6
-68.8
-69.0
-69.2
-69.4
-69.6
-69.8
-70.0
-70.2
-70.4
-70.6
-70.8
-71.0
-71.2
-71.4
-71.6
-71.8
-72.0
f1 (ppm)

5.3 Synthesis of Fragment C7-C18 of E-492

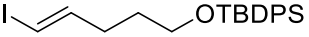
tert-Butyl(pent-4-yn-1-yloxy)diphenylsilane (69)



Compound **69** was prepared according to the previously published procedure.[75] To a solution of pent-4-yn-1-ole **58** (1.00 g, 11.85 mmol) in dichloromethane (25 mL) was added imidazole (1.05 g, 15.46 mmol) and followed by the dropwise addition of TBDPSCl (3.4 mL, 12.84 mmol) at 0 °C and the reaction mixture was stirred for 1 h. Then it was quenched with H_2O (30 mL) and the aqueous phase was extracted with dichloromethane (3×25mL), the combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (1/50 → 1/10 hexane/EtOAc) yielded 3.23 g (86%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.64 (m, 4H), 7.48–7.32 (m, 6H), 3.75 (t, J = 6.0 Hz, 2H), 2.35 (td, J = 7.2, 2.7 Hz, 2H), 1.92 (t, J = 2.7 Hz, 1H), 1.84–1.74 (m, 2H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 134.0, 129.7, 127.8, 84.4, 68.4, 62.4, 31.6, 27.0, 19.4, 15.1. The recorded spectra were in agreement with the published data.[75]

(*E*)-*tert*-Butyl((5-iodopent-4-en-1-yl)oxy)diphenylsilane (70)

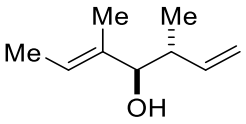


In to a dried flask was added the Schwartz reagent (2.52 g, 9.2 mmol) and diluted with THF (25 mL). After cooling down to 0 °C was added **69** (2.85 g, 8.85 mmol). Then the resulting reaction mixture was warmed up to 22 °C and after being stirred for 100 min, the solution of iodine (6.77 g, 26.54 mmol) in THF (20 mL) was added dropwise. The reaction mixture was quenched with H_2O (15 mL), the aqueous phase was extracted with Et_2O (3×15 mL), the combined organic phases were washed with $Na_2S_2O_3$ (saturated solution, 2×15 mL), H_2O (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 1/5 hexane/Et_2O) yielded 3.21 g (81 %) of the title compound as a slightly pink oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.64 (m, 4H), 7.48–7.37 (m, 6H), 6.50 (dt, J = 14.3, 7.1 Hz, 1H), 5.98 (dt, J = 14.3, 1.4 Hz, 1H), 3.67 (t, J = 6.1 Hz, 2H), 2.28–2.13 (m, 2H), 1.72–1.60 (m, 2H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 135.6, 133.8, 129.6, 127.7, 74.8, 62.7 32.4, 31.1, 26.9; 19.2. IR (KBr) ν_{max} 3419, 2959, 2926, 2890, 2857, 1431, 1108, 937, 824, 704. HRMS (ESI) *m*/*z* calculated for $C_{21}H_{28}OI$ (M+H) 451.09486; measured 451.09503.

5.3.1 Synthesis of Racemate

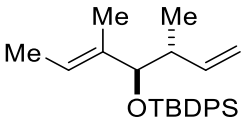
(*E*)-3,5-Dimethylhepta-1,5-dien-4-ol (59)



Compound **59** was prepared according to the previously published procedure.[76] In a dry Schlenk flask were dissolved (*E*)-crotylboronic acid pinacol ester **62** (262 μL, 1.2 mmol) in toluene (2 mL) and followed by addition of tiglic aldehyde **61** (96 μL, 1.0 mmol). After being stirred at 22 °C for 3 days, the reaction mixture was concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of pentane → 20/1 pentane/Et_2O) yielded 110 mg (78%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, J = 17.2, 10.2, 8.4 Hz, 1H), 5.54 (app q, J = 6.6 Hz, 1H), 5.23–5.13 (m, 2H), 3.64 (dd, J = 8.8, 2.0 Hz, 1H), 2.39–2.24 (m, 1H), 1.75 (br s, 1H), 1.65–1.58 (m, 6H), 0.87 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 135.7, 123.0, 116.2, 81.5, 42.2, 16.8, 13.1, 10.6. The recorded spectra were in agreement with the published data.[2]

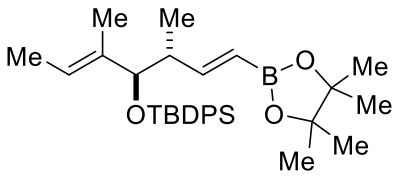
(*E*)-*tert*-Butyl((3,5-dimethylhepta-1,5-dien-4-yl)oxy)diphenylsilane (71)



A solution of **59** (110 mg, 0.78 mmol) in dry DMF (10 mL) was cooled down to 0 °C and imidazole (88 mg, 1.29 mmol), DMAP (4.8 mg, 0.05 mmol) and TBDPSCl (0.69 mL, 2.60 mmol) were added. Then the reaction mixture was warmed up to 80 °C and stirred for seven days. It was quenched by addition of the saturated solution of NH_4Cl (10 mL) and extracted with Et_2O (3×20 mL), the combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexane) yielded 252 mg (85%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.56 (m, 4H), 7.44–7.27 (m, 6H), 5.75 (ddd, J = 17.6, 10.3, 7.5 Hz, 1H), 5.03 (app q, J = 6.6 Hz, 1H), 5.01–4.88 (m, 2H); 3.80 (d, J = 7.9 Hz, 1H), 2.40–2.29 (m, 1H); 1.50–1.45 (m, 3H); 1.34 (dd, J = 6.7, 0.9 Hz, 1H), 1.04 (s, 9H), 0.74 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 136.4, 135.9, 134.6, 134.6, 129.4, 129.3, 127.3, 127.2, 122.8, 114.0, 83.9, 42.8, 27.3, 19.7, 16.3, 12.9, 11.5. IR (KBr) ν_{max} 2962, 2932, 2860, 1434, 1108, 1057, 1042, 914. HRMS (ESI) m/z calculated for $C_{25}H_{34}ONaSi$ (M+Na) 401.22716; measured 401.22711.

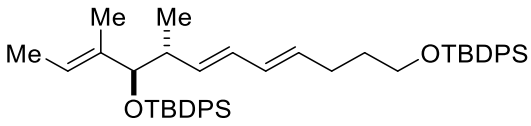
***tert*-Butyl((1*E*,5*E*)-3,5-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,5-dien-4-yl)oxy)diphenylsilane (72)**



In a dry Schlenk flask were dissolved **71** (227 mg, 0.6 mmol) and vinylboronic acid pinacol ester **60** (220 μL, 1.2 mmol) in dichloromethane (20 mL). The solution was degassed by bubbling argon. Meanwhile in a heart flask was dissolved the Hoveyda-Grubbs catalyst II (18 mg, 0.03 mmol) in dichloromethane (10 mL) and the solution was degassed by bubbling argon. The catalyst solution was added dropwise to the previously prepared mixture of vinylboronic acid pinacol ester **60** and **TM94** at 50 °C. The reaction mixture was refluxed for 19 h and then concentrated under reduced pressure. Column chromatography of the residue on silica gel (toluene) yielded 216 mg (71%) of the title compound as a slightly green oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.57 (m, 4H), 7.42–7.27 (m, 6H), 6.63 (dd, J = 18.2, 7.8 Hz, 1H), 5.47 (dd, J = 18.2 Hz, 1H), 4.95 (q, J = 6.5 Hz, 1H), 3.74 (d, J = 8.8 Hz, 1H), 2.48–2.44 (m, 1H), 1.43 (s, 3H), 1.30 (d, J = 6.6 Hz, 3H), 1.26 (s, 12H), 1.01 (s, 9H), 0.70 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 136.5, 136.4, 136.3, 135.4, 134.5, 134.3, 129.4, 129.3, 127.3, 127.1, 123.3, 84.0, 83.0, 44.6, 27.3, 25.0, 24.9, 19.7, 15.8, 12.9, 11.0. IR (KBr) ν_{max} 3470, 3411, 2929, 1643, 1368, 1353, 1320, 1147, 1111, 1057, 973, 704. HRMS (ESI) *m*/*z* calculated for $C_{31}H_{45}O_3BNaSi$ (M+Na) 527.31252; measured 527.31232.

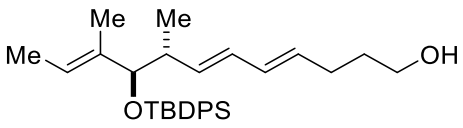
(7*E*,9*E*)-5-((*E*)-But-2-en-2-yl)-2,2,6,16,16-pentamethyl-3,3,15,15-tetraphenyl-4,14-dioxa-3,15-disilaheptadeca-7,9-diene (73)



In a microwave vial were dissolved $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) and iodide **70** (230 mg, 0.51 mmol) in the degassed mixture of THF/H_2O 9/1 (8 mL). Then was added a solution of the compound **72** (284 mg, 0.56 mmol) in the degassed mixture of THF/H_2O 9/1 (5 mL). Then was added TlOEt (0.13 mL 1.87 mmol) with a syringe and the reaction mixture was stirred at 22 °C for 17 h. The reaction mixture was quenched by addition of the saturated solution of NH_4Cl (15 mL) and EtOAc (40 mL). The organic phase was extracted with H_2O (3×20 mL), brine (2×20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 5/1 hexane/toluene) yielded 235 mg (65%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.54 (m, 8H), 7.45–7.27 (m, 12H), 5.96–5.82 (m, 2H), 5.59-5.45 (m, 1H), 5.45–5.33 (m, 1H), 4.99 (q, J = 5.9 Hz, 1H), 3.74 (d, J = 8.0 Hz, 1H), 3.68 (t, J = 6.3 Hz, 2H), 2.40–2.29 (m, 1H), 2.19–2.09 (m, 2H), 1.69–1.59 (m, 2H), 1.48 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.06 (s, 9H), 1.02 (s, 9H), 0.72 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4, 136.4, 136.40, 136.2, 136.0, 135.7, 134.7, 134.3, 131.7, 131.1, 130.1, 129.7, 129.4, 129.3, 127.6, 127.4, 127.3, 127.1, 122.8, 84.1, 63.5, 41.9, 32.6, 29.1, 27.3, 27.0, 19.61, 19.4, 16.7, 12.9, 11.4. IR (KBr) ν_{max} 3073, 2962, 2932, 2887, 2860, 1592, 1422, 1386, 1108, 1051, 988, 824, 740, 704. HRMS (ESI) m/z calculated for $C_{46}H_{60}O_2NaSi_2$ (M+Na) 723.40241; measured 723.40170.

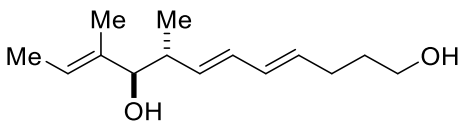
(4*E*,6*E*,10*E*)-9-((*tert*-Butyldiphenylsilyl)oxy)-8,10-dimethyldodeca-4,6,10-trien-1-ol (74)



Into the solution of **73** (30 mg, 0.043 mmol) in THF (2 mL) was added TBAF (1M solution in THF, 86 µL, 0.086 mmol) at 0 °C. Then the reaction mixture was stirred at 30 °C for 4 days. It was quenched with H_2O (5 mL), extracted with EtOAc (3×3 mL), the combined organic phases were washed with brine (2×3 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexane/EtOAc) yielded 12 mg (61%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.55 (m, 4H), 7.42–7.27 (m, 6H), 5.98–5.85 (m, 2H), 5.56–5.46 (m, 1H), 5.44–5.34 (m, 1H), 5.04–4.95 (m, 1H), 3.74 (d, J = 8.2, Hz, 1H), 3.66 (t, J = 6.5, Hz, 2H), 2.38–2.31 (m, 1H), 2.16–2.12 (m, 2H), 1.70–1.62 (m, 2H), 1.48 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.03 (s, 9H), 0.72 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 136.4, 135.9, 134.7, 134.6, 131.5 131.1, 129.9, 129.3, 127.3, 127.3, 127.2, 122.8, 84.1, 62.6, 41.9, 32.5, 31.1, 29.1, 27.3, 16.7, 12.9, 11.3. IR (KBr) νmax. 3333, 2956, 2932, 2054, 1589, 1431, 1111, 1054, 988, 842, 821, 743, 701. HRMS (ESI) m/z calculated for $C_{30}H_{42}O_2NaSi$ (M+Na) 485.28421; measured 485.28463.

(4*E*,6*E*,10*E*)-8,10-Dimethyldodeca-4,6,10-triene-1,9-diol (4)



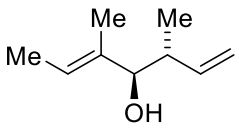
Into the solution of **73** (30 mg, 0.043 mmol) in THF (2 mL) was added TBAF (1M solution in THF, 215 µL, 0.215 mmol) at 0 °C. Then the reaction mixture was stirred at 30 °C for 4 days. It was quenched with H_2O (5 mL), extracted with EtOAc (3×3 mL), the combined organic phases were washed with brine (2×3 mL), dried over $MgSO_4$, and

concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 2/1 hexane/EtOAc) yielded 6 mg (63%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dd, J = 15.0, 10.4 Hz, 1H), 6.10–6.03 (m, 1H), 5.65 (dt, J = 14.4, 7.0 Hz, 1H), 5.52–5.43 (m, 2H), 3.66 (t, J = 6.4 Hz, 2H), 3.62 (d, J = 8.9 Hz, 1H) , 2.34–2.27 (m, 1H), 2.20–2.13 (m, 2H), 1.72 (br s, 1H), 1.70–1.58 (m, 8H); 0.86 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 134.5, 133.0, 132.3, 130.6, 123.7, 82.0, 62.3, 41.4, 32.3, 29.0, 17.3, 13.3, 10.7. IR (KBr) ν_{max} 3437, 3399, 3357, 3016, 2974, 2962, 2926, 1452, 1380, 1057, 1015, 920, 830. HRMS (ESI) m/z calculated for $C_{14}H_{24}O_2Na$ (M+Na) 247.16673; measured 247.16685.

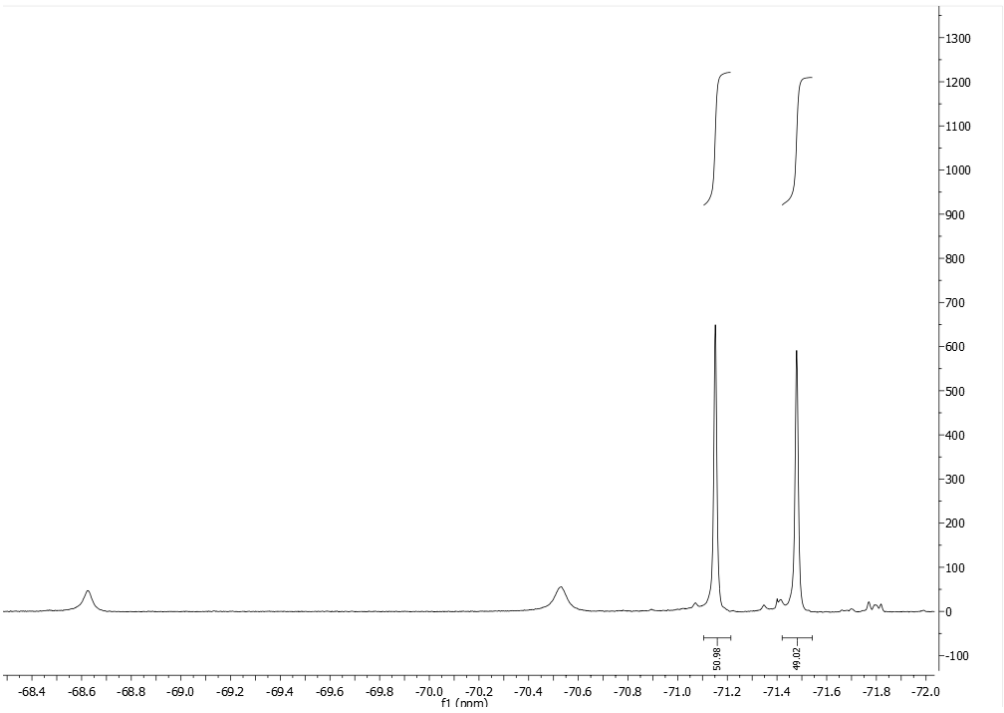
5.3.2 Enantioselective Synthesis

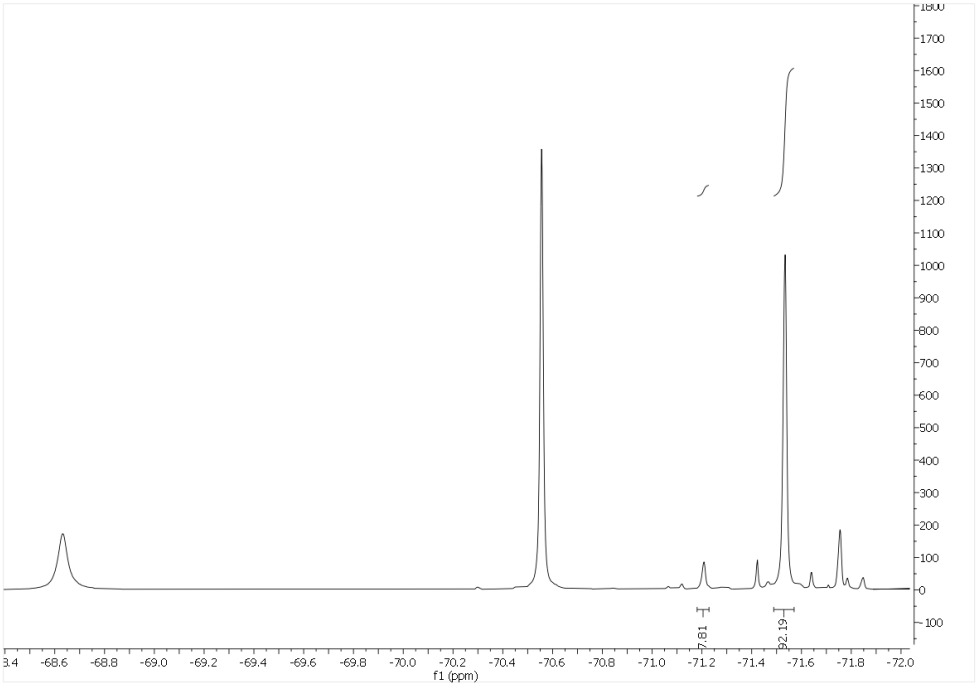
(3*R*,4*R*,*E*)-3,5-Dimethylhepta-1,5-dien-4-ol ((3*R*,4*R*)-59)



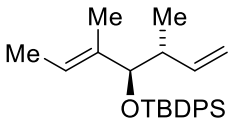
Enantioselective crotylboration on a preparative scale. In a dry Schlenk flask was dissolved (R_a)-TRIP-PA **45** (23 mg, 0.03 mmol) and tyglic aldehyde **61** (120 µL, 1.2 mmol) in dry toluene (8 mL). After cooling down the solution to −60 °C, (*E*)-crotylboronic acid pinacol ester **62** (314 µL, 1.42 mmol) was added. The reaction mixture was stirred at the same temperature for 8 days. It was quenched by DIBAL-H (1M solution in toluene, 1.2 mL) and the reaction mixture was stirred for 30 minutes. Then HCl (1M solution, 1.2 mL) was added and the reaction mixture was warmed up to 22 °C. The aqueous phase was separated and extracted with pentane (2×10 mL), the combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of pentane → 20/1 pentane/Et_2O) yielded 134 mg (76%, 86% ee) of the title compound as a colorless oil.

^1H and ^{13}C NMR spectra correspond with the previously obtained data for **59**. $[\alpha]_D$ = +21.2° ($CHCl_3$, *c* = 1.015).





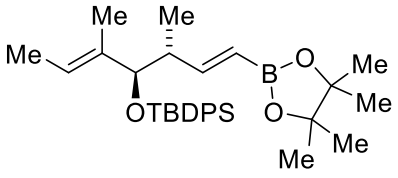
***tert*-butyl(((3*R*,4*R*,*E*)-3,5-Dimethylhepta-1,5-dien-4-yl)oxy)diphenylsilane ((3*R*,4*R*)-71)**



Solution of (3*R*,4*R*)-**59** (350 mg, 2.5 mmol) in dry DMF (12 mL) was cooled down to 0 °C and imidazole (238 mg, 3.3 mmol), DMAP (15 mg, 0.13 mmol) and TBDPSCl (1.84 mL, 7 mmol) were added. Then the reaction mixture was warmed up to 80 °C After seven days the reaction mixture was quenched by the addition of saturated solution of NH_4Cl (10 mL) and extracted with Et_2O (3×15 mL), combined organic phases were washed with brine (10 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexane) yielded 665 mg (71%) of the title compound as a colorless oil.

^1H and ^{13}C NMR spectra correspond with the previously obtained data for **71**. $[\alpha]_D$ = +5.3° ($CHCl_3$, *c* = 0.285).

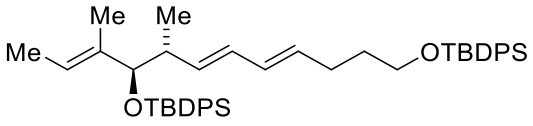
tert-Butyl(((1*E*,3*R*,4*R*,5*E*)-3,5-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,5-dien-4-yl)oxy)diphenylsilane ((3*R*,4*R*)-72)



In a dry Schlenk flask were dissolved (3*R*,4*R*)-**71** (615mg, 1.6 mmol) and vinyl boronic acid pinacol ester **60** (0.60 mL, 3.3 mmol) in dichloromethane (20 mL). The solution was degassed by bubbling argon. Meanwhile in the heart flask was dissolved the Hoveyda-Grubbs catalyst II (51.5 mg, 0.08 mmol) in dichloromethane (10 mL) and the solution was degassed by bubbling argon. The catalyst solution was added dropwise to the previously prepared mixture of vinylboronic acid pinacol ester **60** and (3*R*,4*R*)-**59** at 50 °C. The reaction mixture was refluxed for 19 h and then concentrated under reduced pressure. Column chromatography of the residue on silica gel (toluene) yielded 717 mg (86%) of the title compound as a colorless oil.

^{1}H and ^{13}C NMR spectra correspond with the previously obtained data for **72**. $[\alpha]_D = -12.3°$ ($CHCl_3$, $c = 0.325$).

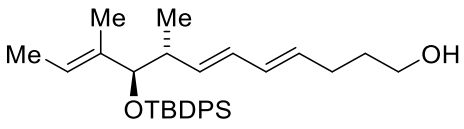
(5*R*,6*R*,7*E*,9*E*)-5-((*E*)-But-2-en-2-yl)-2,2,6,16,16-pentamethyl-3,3,15,15-tetraphenyl-4,14-dioxa-3,15-disilaheptadeca-7,9-diene ((5*R*,6*R*)-73)



In a microwave vial were dissolved $Pd(PPh_3)_4$ (15.5 mg, 0.013 mmol) and iodide **70** (120 mg, 0.27 mmol) in the degassed mixture of THF/H_2O 9/1 (8 mL). Then was added a solution the boronate (3*R*,4*R*)-**72** (148 mg, 0.29 mmol) in the degassed mixture of THF/H_2O 9/1 (5 mL). Then was added TlOEt (41µL, 0.58 mmol) with a syringe and the reaction mixture was stirred at 22 °C for 17 h. The reaction mixture was quenched by addition of the saturated solution of NH_4Cl (5 mL) and EtOAc (10 mL). The organic phase was extracted with H_2O (3×5 mL), brine (2×5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 5/1 hexane/toluene) yielded 113 mg (61%) of the title compound as a colorless oil.

^{1}H and ^{13}C NMR spectra were in agreement with obtained data for **73**. $[\alpha]_D = -31.3°$($CHCl_3$, $c = 1.375$).

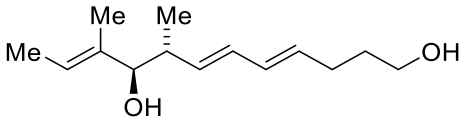
(4*E*,6*E*,8*R*,9*R*,10*E*)-9-((*tert*-Butyldiphenylsilyl)oxy)-8,10-dimethyldodeca-4,6,10-trien-1-ol ((8*R*,9*R*)-74)



Into a solution of (5*R*,6*R*)-**73** (103 mg, 0.147 mmol) in THF (5 mL) was added TBAF (1M solution in THF, 0.747 mL, 0.747 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 4 days. It was quenched with H_2O (6 mL), extracted with EtOAc (3×5 mL), the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 10/1 hexane/EtOAc) yielded 20 mg (30%) of the title compound as a colorless oil.

^{1}H and ^{13}C NMR spectra were in agreement with obtained data for **74**. $[\alpha]_D = -26.8°$ ($CHCl_3$, $c = 0.84$).

(4*E*,6*E*,8*R*,9*R*,10*E*)-8,10-Dimethyldodeca-4,6,10-triene-1,9-diol ((8*R*,9*R*)-4)



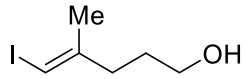
Into a solution of (5*R*,6*R*)-**73** (103 mg, 0.147 mmol) in THF (5 mL) was added TBAF (1M solution in THF, 0.747 mL, 0.747 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 4 days. The reaction mixture was quenched with H_2O (6 mL), extracted with EtOAc (3×5 mL) and the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 2/1 hexane/EtOAc), followed by column chromatography (3/1 toluene/EtOAc → 2/1 toluene/EtOAc) and followed by preparative TLC (1/1 EtOAc/hexane) yielded 9.4 mg (34%) of the title compound as a colorless oil.

^{1}H and ^{13}C NMR spectra were in agreement with obtained data for **4**. $[\alpha]_D = +23.4°$ ($CHCl_3$, $c = 0.47$).[III]

[III] Research for the best condition to determine the enantioselectivity was still ongoing process when the thesis was submited, therefore it is not covered within this work.

5.4 Synthesis of Fragment C7-C18 of Actinofuranone A

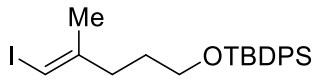
(*E*)-5-Iodo-4-methylpent-4-en-1-ol (63)



Iodide **63** was prepared according to the previously published procedure.[74] Iodine was purified by sublimation from the mixture of I_2 (65%), KI (25%), and BaO (10%), 4-pentyn-1-ol **58** was distilled and Cp_2ZrCl_2 was dried under the vacuum at 50 °C for 2 h. A solution of Cp_2ZrCl_2 (438 mg, 1.5 mmol) in dichloromethane (3 mL) was cooled down to 0°C. Then the Me_3Al (2M solution in hexane, 2.25 mL, 4.5 mmol) was added and the reaction mixture was warmed up to 22 °C. After being stirred for 2 h, the mixture was cooled down to -20 °C and then the solution of 4-pentyn-1-ol **58** (139 μL, 1.5 mmol) in dichloromethane (2 mL) was added dropwise over 15 min. The cold bath was removed, and the reaction mixture was stirred overnight. Then the reaction mixture was cooled down to -40 °C, iodine (505 mg, 1.96 mmol) in THF (4 mL) was added and warmed up to 22 °C. After the reaction mixture being stirred for 90 min, it was cooled down to 0 °C and quenched by a very slow addition of H_2O (10 mL). Et_2O (10 mL) was added to this solution and the reaction mixture was filtered through a Celite pad. The aqueous phase was diluted with 1M HCl (5 mL) and extracted with Et_2O (15 mL). The combined organic layers were washed with $NaHCO_3$ (sat. solution, 8 mL), Rochelle's salt (sat. solution, 8 mL), brine (8 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 1/2 hexane/Et_2O) yielded 150 mg (45%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (q, J = 1.0 Hz, 1H), 3.63 (t, J = 6.4 Hz, 2H), 2.33–2.26 (m, 2H), 1.84 (d, J = 1.0 Hz, 3H), 1.75–1.66 (m, 2H), 1.51 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.58, 75.10, 62.17, 35.89, 30.66, 23.96. HRMS (ESI) m/z calculated for $C_6H_{12}OI$ (M+H) 226.99273; measured 226.99286. The recorded spectra were in agreement with the published data.[77]

(*E*)-*tert*-Butyl((5-iodo-4-methylpent-4-en-1-yl)oxy)diphenylsilane (75)

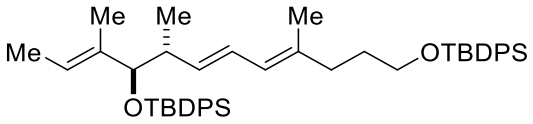


Compound **75** was prepared according to the previously published procedure.[77] The solution of **63** (117 mg, 0.518 mmol) and imidazole (64 mg, 0.94 mmol) in dichloromethane (5 mL) in a Schlenk flask was cooled down to 0 °C. Then the TBDPSCl (234 μL, 0.854 mmol) was added dropwise. The reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched by addition of the saturated solution of NH_4Cl (5 mL) and extracted with

dichloromethane (3×10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 1/50 hexane/EtOAc) yielded 192 mg (81%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 4H) 7.48–7.34 (m, 6H), 5.88–5.83 (m, 1H), 3.63 (t, J = 6.2 Hz, 2H), 2.34–2.27 (m, 2H), 1.80 (d, J = 1.1 Hz, 3H), 1.74–1.62 (m, 2H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 135.7, 134.0, 129.7, 127.8, 74.9, 63.0, 35.9, 30.7, 27.0, 24.0, 19.4. HRMS (ESI) m/z calculated for $C_{22}H_{30}OISi$ (M+H) 465.11051; measured 465.11051. The recorded spectra were in agreement with the published data.[77]

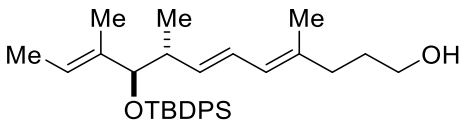
5.4.1 Synthesis of racemate (7*E*,9*E*)-5-((*E*)-But-2-en-2-yl)-2,2,6,10,16,16-hexamethyl-3,3,15,15-tetraphenyl-4,14-dioxa-3,15-disilaheptadeca-7,9-diene (76)



In a microwave vial were dissolved $Pd(PPh_3)_4$ (6 mg, 0.005 mmol), iodide **75** (47 mg, 0.1 mmol) and boronate **72** (55 mg 0.11 mmol) in the degassed mixture of THF/H_2O 9/1 (8 mL). Then was added TlOEt (30 µL, 0.3 mmol) with a syringe and the reaction mixture was stirred at 22 °C for 17 h. The reaction mixture was quenched by addition of the saturated solution of NH_4Cl (5 mL) and EtOAc (10 mL). The organic phase was extracted with H_2O (3×5 mL), brine (2×5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 5/1 hexane/toluene) yielded 55 mg (75%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.53 (m, 8H), 7.46–7.27 (m, 12H), 6.14 (dd, J = 15.1, 10.8 Hz, 1H), 5.68 (d, J = 10.8 Hz, 1H), 5.28 (dd, J = 15.1, 8.3 Hz, 1H), 5.05–4.90 (m, 1H), 3.75 (d, J = 8.1 Hz, 1H), 3.67 (t, J = 6.4 Hz, 2H), 2.48–2.27 (m, 1H), 2.13–2.07 (m, 2H), 1.74–1.63 (m, 5H), 1.50 (s, 3H), 1.37 (d, J = 7.3 Hz, 3H), 1.06 (s, 9H), 1.01 (s, 9H), 0.73 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 136.4, 136.2, 136.0, 135.7, 134.6, 134.3, 129.7, 129.4, 129.3, 127.7, 127.3, 127.1, 126.5, 125.3, 122.7, 84.1, 63.8, 42.4, 36.2, 31.2, 27.3, 27.0, 19.6, 19.4, 16.9, 16.7, 12.9, 11.4.

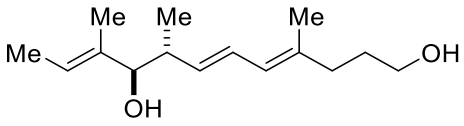
(4*E*,6*E*,10*E*)-9-((*tert*-Butyldiphenylsilyl)oxy)-4,8,10-trimethyldodeca-4,6,10-trien-1-ol (77)



Into a solution of **76** (34 mg, 0.048 mmol) in THF (2 mL) at 0 °C was added TBAF (1M solution in THF, 241 μL, 0.241 mmol). Then the reaction mixture was stirred at 22 °C for 4 days. It was quenched with H_2O (4 mL), extracted with EtOAc (3×5 mL) and the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 10/1 hexane/EtOAc) yielded 13 mg (57%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.53 (m, 4H), 7.46–7.25 (m, 6H), 6.16 (dd, J = 15.1, 10.8 Hz, 1H), 5.72 (d, J = 10.8 Hz, 1H), 5.32 (dd, J = 15.1, 8.3 Hz, 1H), 5.05–4.95 (m, 1H), 3.75 (d, J = 8.2 Hz, 1H), 3.63 (t, J = 6.5 Hz, 2H), 2.45–2.30 (m, 1H), 2.12 (t, J = 7.3 Hz, 2H), 1.76 – 1.64(m, 5H), 1.49 (s, 3H), 1.36 (d, J = 6.1 Hz, 3H), 1.02 (s, 9H), 0.72 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 136.5, 136.4, 135.9, 135.5, 134.7, 129.3, 127.3, 127.1, 126.4, 125.7, 122.8, 84.1, 62.9, 42.3, 36.2, 30.9, 27.3, 19.6, 16.9, 16.5, 12.9, 11.3.

(4*E*,6*E*,10*E*)-4,8,10-Trimethyldodeca-4,6,10-triene-1,9-diol (5)

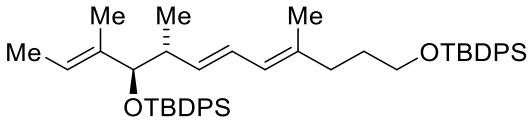


Into a solution of **76** (34 mg, 0.048 mmol) in THF (2 mL) was added TBAF (1M solution in THF, 241 μL, 0.241 mmol) at 0 °C. Then the reaction mixture was stirred at 22 °C for 4 days. It was quenched with H_2O (4 mL), extracted with EtOAc (3×5 mL), the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 2/1 hexane/EtOAc) yielded 4 mg (35%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, J = 15.1, 11.7 Hz, 1H), 5.86 (d, J = 10.8 Hz, 1H), 5.54–5.40 (m, 2H), 3.68–3.58 (m, 3H), 2.41–2.27 (m, 1H), 2.13 (t, J = 7.2 Hz, 2H), 1.81–1.66 (m, 6H), 1.66–1.57 (m, 6H), 0.89 (d, J = 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 135.7,134.5, 128.7, 124.8, 123.6, 82.1, 62.8, 41.8, 36.2, 30.9, 17.4, 16.7, 13.3, 10.7.

5.4.2 Enantioselective synthesis

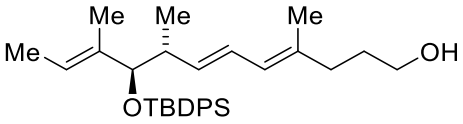
(5*R*,6*R*,7*E*,9*E*)-5-((*E*)-But-2-en-2-yl)-2,2,6,10,16,16-hexamethyl-3,3,15,15-tetraphenyl-4,14-dioxa-3,15-disilaheptadeca-7,9-diene ((5*R*,6*R*)-76)



In a microwave vial were dissolved $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), iodide **75** (98 mg 0.21 mmol) and boronate (3*R*,4*R*)-**72** (118 mg, 0.23 mmol) in the degassed mixture of THF/H_2O 9/1 (8 mL). Then was added TlOEt (45 μL, 0.6 mmol) with a syringe and the reaction mixture was stirred at 22 °C for 17 h. The reaction mixture was quenched by addition of the saturated solution of NH_4Cl (5 mL) and EtOAc (10 mL). The organic phase was extracted with H_2O (3×5 mL), brine (2×5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 5/1 hexane/toluene) yielded 90 mg (60%) of the title compound as a colorless oil.

^1H and ^{13}C NMR spectra were in agreement with obtained data for **76**. $[\alpha]_D = -18.8°$ ($CHCl_3$, $c = 0.665$).

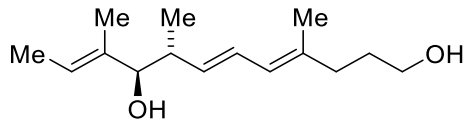
(4*E*,6*E*,8*R*,9*R*,10*E*)-9-((*tert*-Butyldiphenylsilyl)oxy)-4,8,10-trimethyldodeca-4,6,10-trien-1-ol ((8*R*,9*R*)-77)



Into the solution of (8*R*,9*R*)-**76** (81 mg, 0.11 mmol) in THF (4 mL) was added TBAF (1M solution in THF, 0.57 mL, 0.57 mmol) at 0 °C. Then the reaction mixture was stirred at 25 °C for 4 days. It was quenched by the addition of H_2O (6 mL), extracted with EtOAc (3×5 mL), the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 10/1 hexane/EtOAc) yielded 22 mg (41%) of the title compound as a colorless oil.

^1H and ^{13}C NMR spectra were in agreement with obtained data for **77**. $[\alpha]_D = -40.8°$ ($CHCl_3$, $c = 0.845$).

(4*E*,6*E*,8*R*,9*R*,10*E*)-4,8,10-Trimethyldodeca-4,6,10-triene-1,9-diol ((8*R*,9*R*)-5)

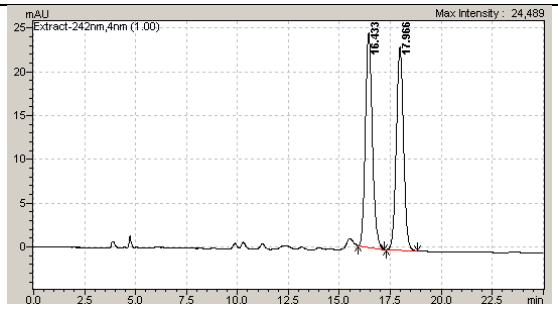


Into the solution of (8*R*,9*R*)-**76** (81 mg, 0.11 mmol) in THF (4 mL) was added TBAF (1M solution in THF, 0.57 mL, 0.57 mmol) at 0 °C. Then the reaction

mixture was stirred at 22 °C for 4 days. It was quenched with H_2O (6 mL), extracted with EtOAc (3×5 mL), the combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 2/1 hexane/EtOAc) yielded 14 mg (51%, 85% ee) of the title compound as a colorless oil.

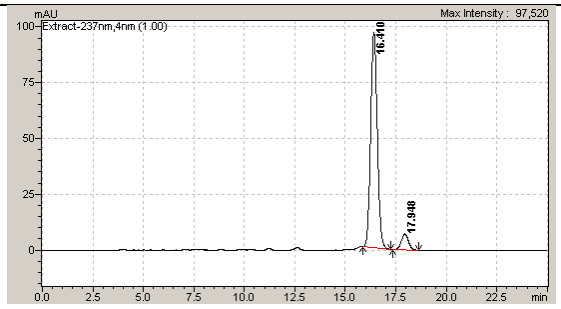
^1H and ^{13}C NMR spectra were in agreement with obtained data for **5**. $[\alpha]_D$ = +27.9° ($CHCl_3$, *c* = 0.680). HPLC analysis: 7:93 e.r. (column DC IA: Heptane/*i*-PrOH = 95/5, flow rate 0.5 mL/min, t_{major} = 16.4 min; t_{minor} = 17.9 min)

5



N°	Retention time (min)	Relative area (%)
1	16.4	50.4
2	17.9	49.6

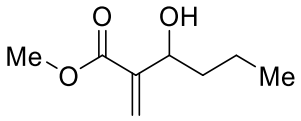
(8*R*,9*R*)-**5**



N°	Retention time (min)	Relative area (%)
1	16.4	92.6
2	17.9	7.4

5.5 Synthesis of Fragment C7-C20 of JBIR-108

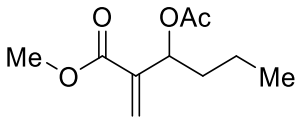
Methyl 3-hydroxy-2-methylenehexanoate (79)



Compound **79** was prepared according to the previously published procedure.[2] To a solution of butanal **79** (7.21 g, 100 mmol) in methyl acrylate (14 mL, 150 mmol) at 22 °C was added DABCO (1.68 g, 15.0 mmol). Afterward, the resulting mixture was stirred for 13 days at the same temperature and concentrated under reduced pressure. The residue was washed with 1 M HCl (30 mL), H_2O (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 12.6 g (80%) of the title compound as a colorless oil, which was used for the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) 6.22 – 6.20 (m, 1H), 5.79 (t, J = 1.0 Hz, 1H), 5.81–5.76 (m, 1H), 3.77 (s, 3H), 2.56 (br s, 1H), 1.67 – 1.58 (m, 2H), 1.52–1.30 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 142.6, 125.1, 71.7, 52.0, 38.5, 19.2, 14.0. HRMS (ESI) m/z calculated for $C_8H_{14}O_3Na$ (M+Na) 181.08352; measured 181.08357. The recorded spectra were in agreement with the published data.[78]

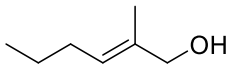
Methyl 3-acetoxy-2-methylenehexanoate (80)



Compound **80** was prepared according to the previously published procedure.[2] To a stirred solution of **79** (12.16 g, 76.9 mmol) in toluene (76 mL) at 0 °C, DMAP (0.94 g, 7.7 mmol) and Ac_2O (8.7 mL, 92.2 mmol) were added. The resulting mixture was stirred at 22 °C for 19 h. Then 1 M HCl (22 mL) was added to quench the reaction mixture. The resulting mixture was washed with H_2O (30 mL), $NaHCO_3$ (the saturated solution, 30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 13.83 g (91%) of the title compound as a colorless oil, which was used for the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (s, 1H), 5.77–5.72 (m, 1H), 5.65–5.58 (m, 1H), 3.77 (s, 3H), 2.07 (s, 3H), 1.79–1.63 (m, 2H), 1.44–1.27 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 165.9, 140.4, 125.2, 71.8, 52.1, 36.6, 21.2, 18.8, 13.9. HRMS (ESI) m/z calculated for $C_{10}H_{16}O_4Na$ (M+Na) 223.09408; measured 223.09384. The recorded spectra were in agreement with the published data.[79]

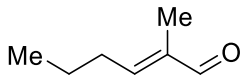
(*E*)-2-Methylhex-2-en-1-ol (81)



Compound **81** was prepared according to the previously published procedure.[2] To a solution of $LiAlH_4$ (1M solution in THF, 33.56 mmol, 33.56 mL) stirred at -78 °C, dry EtOH (2.4 mmol, 1.95 mL) and solution of **80** (13.98 mmol, 2.80g) in dry Et_2O (40 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 40 min. To quench the reaction mixture, H_2O (8 mL) was added and the reaction mixture was warmed up to 22 °C. The resulting mixture was filtered through a pad of Celite, dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc →10/1 hexane/EtOAc) yielded 1.10 g (73%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45–5.34 (m, 1H), 4.00 (d, J = 5.5 Hz, 2H), 2.06–1.95 (m, 2H), 1.63 (s, 3H), 1.44–1.31 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 126.3, 70.0, 29.8, 22.8, 13.9, 13.7. The recorded spectra were in agreement with the published data.[2]

(*E*)-2-Methylhex-2-enal (64)

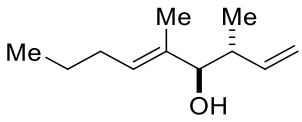


64 was prepared according to the previously published procedure.[2] In a Schlenk flask, to a solution of DMSO (1.48 mL, 21.0 mmol) in dry dichloromethane (35 mL) at -78 °C was added $(COCl)_2$ (1.6 mL, 18.2 mmol) and the reaction mixture was stirred at the same temperature for 15 min. Then a solution of **81** (1.01 mg, 9.3 mmol) in dry dichloromethane (10 mL) was added to the reaction mixture and stirred at the same temperature. After 30 min Et_3N (3.9 mL, 27.7 mmol) was added and the reaction mixture was warmed up to 22 °C and stirred for another 30 min. The reaction mixture was quenched with the saturated solution of NH_4Cl (30 mL), extracted with dichloromethane (3×20 mL), the combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexane/EtOAc 1/20) yielded 613 mg (81%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 6.49 (t, J = 7.4 Hz, 1H), 2.40–2.28 (m, 2H), 1.74 (s, 3H), 1.62–1.47 (m, 2H), 0.97 (t, J = 7.3 Hz, 3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6, 154.9, 139.7, 31.1, 21.9, 14.0, 9.4. The recorded spectra were in agreement with the published data.[2]

5.5.1 Synthesis of racemate

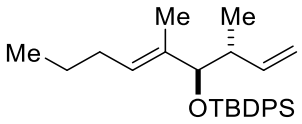
(*E*)-3,5-Dimethylnona-1,5-dien-4-ol (65)



In a dry Schlenk flask, the previously prepared aldehyde **64** (189 mg, 1.7 mmol) was dissolved in toluene (5 mL) and followed by addition of (*E*)-crotylboronic acid pinacol ester **62** (345 µL, 2.0 mmol). After being stirred at 22 °C for 4 days, the reaction mixture was concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of pentane → 40/1 pentane/Et_2O) yielded 193 mg (68%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddd, J = 17.2, 10.2, 8.4 Hz, 1H), 5.40 (t, J = 7.1 Hz, 1H), 5.20–5.11 (m, 2H), 3.64 (dd, J = 8.8, 2.3 Hz, 1H), 2.38–2.24 (m, 1H), 2.09–1.97 (m, 2H), 1.74 (d, J = 2.4 Hz, 1H), 1.61 (s, 3H), 1.45–1.34 (m, 2H), 0.93–0.86 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 134.9, 129.4, 116.6, 81.7, 42.4, 29.8, 22.8, 17.0, 14.0, 11.1. The recorded spectra were in agreement with the published data.[2]

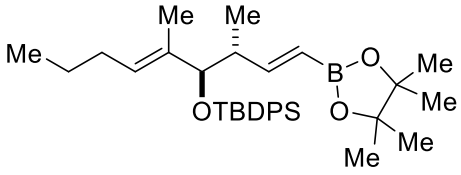
***tert*-Butyl(((3*R*,4*R*,*E*)-3,5-dimethylnona-1,5-dien-4-yl)oxy)diphenylsilane (82)**



A solution of **65** (181 mg, 1.07 mmol) in dry DMF (12 mL) was cooled down to 0 °C and imidazole (102 mg, 1.51 mmol), DMAP (7 mg, 0.05 mmol) and TBDSPCl (0.80 mL, 3.01 mmol) were added. Then the reaction mixture was warmed up to 80 °C and stirred for seven days. It was quenched by addition of NH_4Cl (saturated solution, 7 mL) and extracted with Et_2O (3×15 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexane) yielded 330 mg (75%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.60 (m, 4H), 7.45–7.30 (m, 6H), 5.73 (ddd, J = 17.9, 10.4, 7.6 Hz, 1H), 5.05–4.86 (m, 3H), 3.83 (d, J = 7.7 Hz, 1H), 2.40–2.29 (m, 1H), 1.94–1.64 (m, 2H) 1.49 (s, 3H), 1.29–1.16 (m, 2H), 1.07 (s, 9H), 0.83 (t, J = 7.4 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ. 142.6, 136.4, 135.1, 134.7, 134.6, 129.5, 129.4, 128.7, 127.3, 127.2, 114.0, 83.9, 42.9, 29.6, 27.3, 22.5, 19.7, 16.3, 14.0, 12.0. IR (KBr) ν_{max} 3072, 2958, 2858, 1486, 1429, 1361 1047, 739, 698, 612, 501.

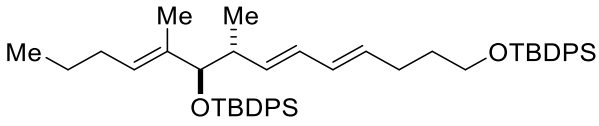
tert-Butyl(((1*E*,5*E*)-3,5-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nona-1,5-dien-4-yl)oxy)diphenylsilane (83)



In a dry Schlenk flask were dissolved **82** (298mg, 0.73 mmol) and vinylboronic acid pinacol ester **60** (0.27 mL, 1.46 mmol) in dichloromethane (10 mL). The solution was degassed by bubbling argon. Meanwhile in a heart flask was dissolved the Hoveyda-Grubbs catalyst II (23 mg, 0.04 mmol) in dichloromethane (10 mL) and the solution was degassed by bubbling argon. The catalyst solution was added dropwise to the previously prepared mixture of vinylboronic acid pinacol ester **60** and **82** at 50 °C. The reaction mixture was refluxed for 20 h and then concentrated under reduced pressure. Column chromatography of the residue on silica gel (toluene) yielded 365 mg (93%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.58 (m, 4H), 7.44–7.27 (m, 6H), 6.61 (dd, J = 18.0, 7.7 Hz, 1H), 5.44 (dd, J = 18.0, 1.0 Hz, 1H), 4.90 (t, J = 6.6 Hz, 1H), 3.78 (d, J = 8.4 Hz, 1H), 2.53–2.39 (m, 1H), 1.83– .61 (m, 2H), 1.45 (s, 3H), 1.23 (d, J = 2.9 Hz, 12H), 1.20–1.13 (m, 1H), 1.02 (s, 9H), 0.77 (t, J = 7.3 Hz, 3H), 0.73 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 136.4, 137.7, 134.6, 134.4, 129.4, 129.3, 129.1, 127.3. 127.2, 83.9, 83.0, 44.7, 29.6, 27.4, 25.0, 24.9, 22.5, 19.7, 15.8, 14.0, 11.6. IR (KBr) ν_{max} 2958, 2854, 1638, 1359, 1318, 1144, 1049, 970, 739, 701, 612, 509.

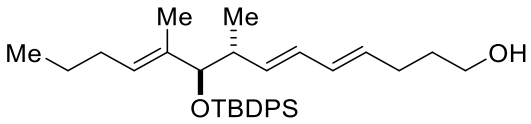
(7*E*,9*E*)-5-((*E*)-hex-2-en-2-yl)-2,2,6,16,16-Pentamethyl-3,3,15,15-tetraphenyl-4,14-dioxa-3,15-disilaheptadeca-7,9-diene (84)



In a microwave vial were dissolved $Pd(PPh_3)_4$ (34 mg, 0.03 mmol) and iodide **70** (265 mg, 0.59 mmol) in the degassed mixture of THF/H_2O 9/1 (5 mL). Then was added a solution the boronate **83** (327 mg, 0.65 mmol) in the degassed mixture of THF/H_2O 9/1 (8 mL). Then was added TlOEt (90µL, 1.29 mmol) with a syringe and the reaction mixture was stirred at 22 °C for 40 h. The reaction mixture was quenched by addition of the saturated solution of NH_4Cl (15 mL) and EtOAc (30 mL). The organic phase was extracted with H_2O (3×10 mL), brine (2×10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 5/1 hexane/toluene) yielded 290 mg (67%) of the title compound as a colorless oil.

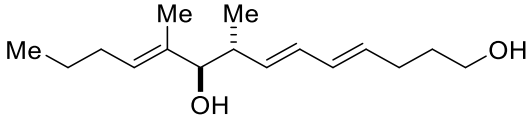
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.55 (m, 8H), 7.47–7.27 (m, 12H), 5.91–5.80 (m, 2H), 5.47 (dt, J = 13.6, 6.9 Hz, 1H), 5.39–5.27 (m, 1H), 4.97 (t, J = 6.6 Hz, 1H), 3.76 (d, J = 7.9 Hz, 1H), 3.72–3.64 (m, 2H), 2.42–2.30 (m, 1H), 2.14 (q, J = 7.1 Hz, 2H), 1.88–1.71 (m, J = 7.1 Hz, 2H), 1.73–1.59 (m, 2H), 1.51 (s, 3H), 1.23 (ddt, J = 10.4, 7.3, 3.1 Hz, 2H), 1.06 (s, 9H), 1.02 (d, J = 2.9 Hz, 9H), 0.85–0.78 (m, 3H), 0.73 (dd, J = 6.8, 3.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 136.4, 136.2, 135.7, 135.2, .134.7, 134.6, 134.3, 131.7, 131.1, 130.1, 129.7, 129.4, 128.6, 127.7, 127.3, 127.2, 84.0, 63.5, 50.0, 32.6, 29.6, 29.1, 27.3, 27.0, 22.6, 19.6, 19.4, 16.8, 14.1, 11.9. .IR (KBr) ν_{max} 3071, 2957, 2857, 1472, 1427, 1105, 822, 738, 699, 611, 502.

(4*E*,6*E*,10*E*)-9-((*tert*-Butyldiphenylsilyl)oxy)-8,10-dimethyltetradeca-4,6,10-trien-1-ol (85)



Into a solution of **84** (167 mg, 0.23 mmol) in THF (4 mL) was added TBAF (1M solution in THF, 1.14 mL, 1.14 mmol) at 0 °C. Then the reaction mixture was stirred at 23 °C for 4 days. It was quenched with H_2O (5 mL), extracted with EtOAc (3×3 mL), the combined organic phases were washed with brine (2×3 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 10/1 hexane/EtOA) yielded 49 mg (45%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.55 (m, 4H), 7.45–7.26 (m, 6H), 5.93–5.87 (m, 2H), 5.55–5.45 (m, 1H), 5.55–5.45 (m, 1H), 4.97 (q, J = 6.6 Hz, 1H), 3.75 (d, J = 8.0 Hz, 1H), 3.65 (t, J = 6.5 Hz, 2H), 2.44–2.28 (m, 1H), 2.19–2.08 (m, 2H), 1.84–1.73 (m, 2H), 1.71–1.61 (m, 2H), 1.51 (s, 3H), 1.31–1.16 (m, 2H), 1.03 (s, 9H), 0.81 (t, J = 7.4 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$). δ 136.7, 136.4, 135.1, 134.7, 134.6, 131.5, 131.1, 129.9, 129.4, 128.7, 127.7, 127.2, 84.0, 62.7, 42.0 35.5, 29.6, 27.3, 22.6, 19.6, 14.1, 11.8.

(4*E*,6*E*,10*E*)-8,10-Dimethyltetradeca-4,6,10-triene-1,9-diol (6)



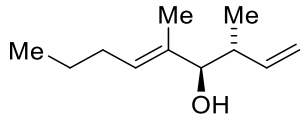
Into a solution of **84** (167 mg, 0.23 mmol) in THF (4 mL) was added TBAF (1M solution in THF, 1.14 mL, 1.14 mmol) at 0 °C. Then the reaction mixture was stirred at 23 °C for 5 days. It was quenched with H_2O (5 mL), extracted with EtOAc (3×3 mL), the combined organic phases were washed with brine (2×3 mL), dried over

$MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc → 2/1 hexane/EtOAc) yielded 13 mg (32%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20–6.00 (m, 2H), 5.64 (dt, J = 13.8, 7.0 Hz, 1H), 5.48 (dd, J = 14.7, 8.6 Hz, 1H), 5.39 (t, J = 7.3 Hz, 1H), 3.70–3.61 (m, 3H), 2.37–2.26 (m, 1H), 2.16 (dt, J = 11.3, 5.9 Hz, 1H), 2.02 (dt, J = 14.4, 7.2 Hz, 2H), 1.72–1.62 (m, 3H), 1.60 (s, 3H), 1.39 (ddt, J = 10.5, 7.3, 3.1 Hz, 2H), 0.96–0.83 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0, 134.6, 133.0, 132.2, 130.7, 129.4, 82.1, 62.6, 41.4, 32.3, 29.8, 29.0, 22.8, 17.3, 14.0, 11.0.

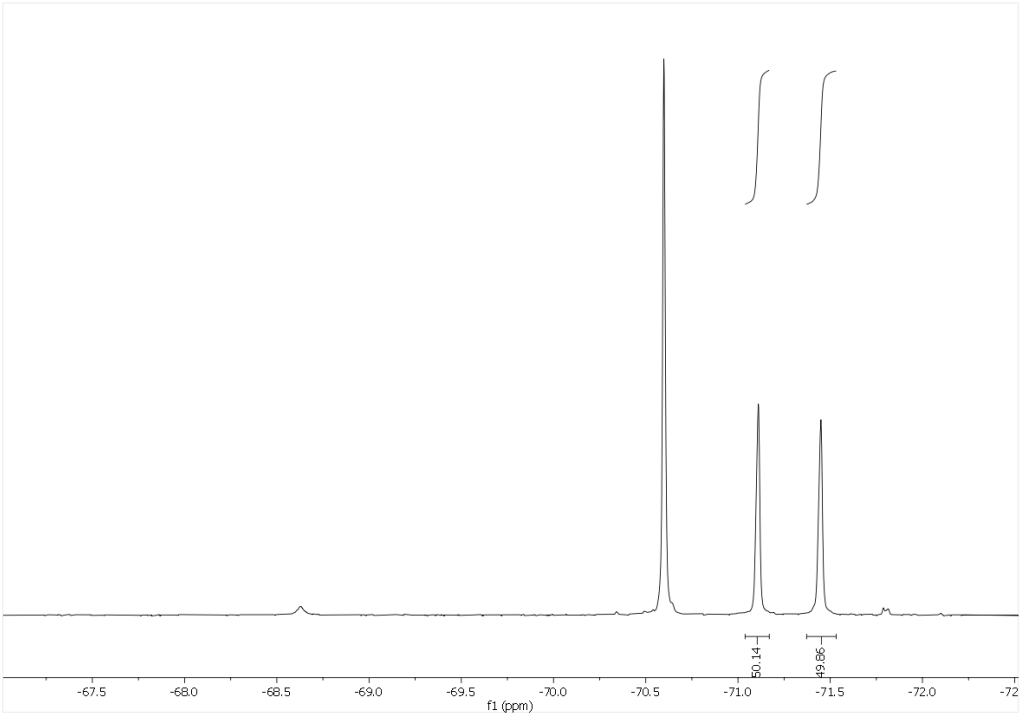
5.5.2 Enantioselective Synthesis

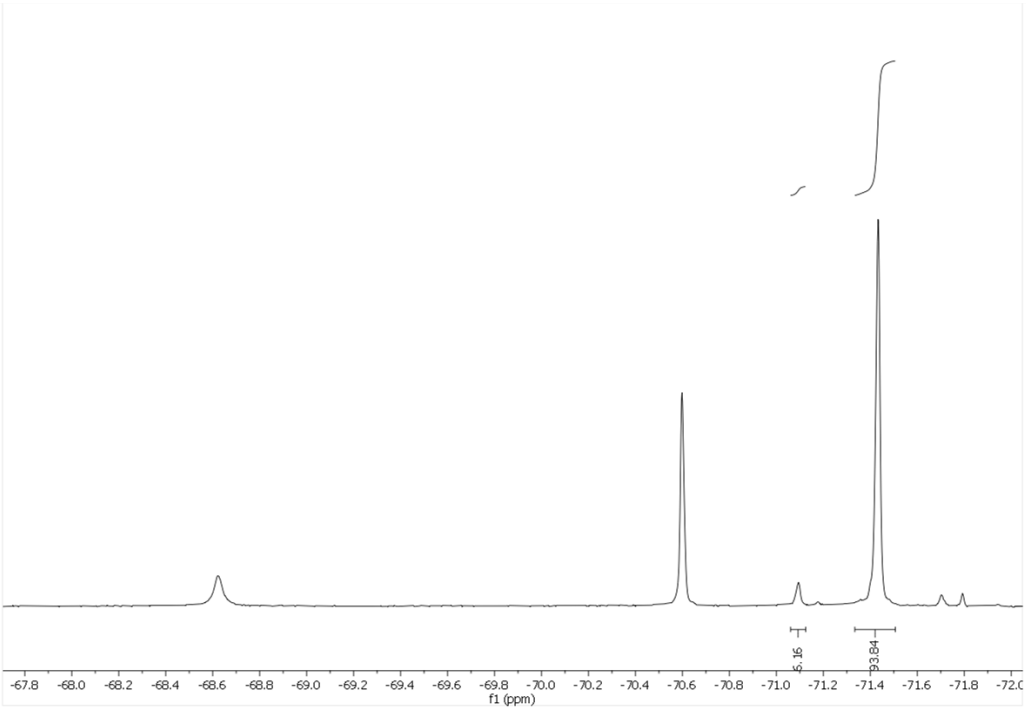
(3*R*,4*R*,*E*)-3,5-Dimethylnona-1,5-dien-4-ol ((3*R*,4*R*)-65)



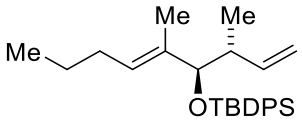
Enantioselective crotylboration on a preparative scale. In a dry Schlenk flask were dissolved (R_a)-TRIP-PA (45 mg, 5 mol%) and crotyl boronate **62** (318 µL, 1.44 mmol) in toluene (8mL). After cooling down the solution to −60 °C, the aldehyde **64** was divided into five parts (27 mg, totally 135 mg, 1.2 mmol) and every 24 for hours was added one part. Then the reaction was stirred for additional 4 days at the same temperature. To quench the reaction DIBAL-H (1M solution in toluene, 1.5 mL) was added to the reaction and the reaction mixture was stirred for 30 minutes. Then HCl (1M solution, 1.5 mL) was added and the reaction was warmed up to 22 °C. The aqueous phase was separated and extracted with pentane (2x10mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of pentane → 20/1 pentane/Et_2O) yielded 145 mg (72%, 88% ee) of the title compound as a colorless oil.

^{1}H and ^{13}C NMR spectra were in agreement with obtained data for **65**. $[\alpha]_D$ = +12.5° ($CHCl_3$, c = 1.640).


50.14
49.86
-67.5
-68.0
-68.5
-69.0
-69.5
-70.0
-70.5
-71.0
-71.5
-72.0
f1 (ppm)


6.16
93.84
-67.8
-68.0
-68.2
-68.4
-68.6
-68.8
-69.0
-69.2
-69.4
-69.6
-69.8
-70.0
-70.2
-70.4
-70.6
-70.8
-71.0
-71.2
-71.4
-71.6
-71.8
f1 (ppm)

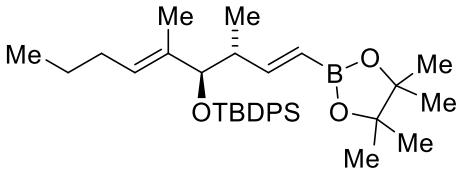
***tert*-Butyl(((3*R*,4*R*,*E*)-3,5-dimethylnona-1,5-dien-4-yl)oxy)diphenylsilane ((3*R*,4*R*)-82)**



A solution of (3*R*,4*R*)-**65** (231 mg, 1.37 mmol) in dry DMF (15 mL) was cooled down to 0 °C and imidazole (131 mg, 1.92 mmol), DMAP (8 mg, 0.07 mmol) and TBDSPSCl (1.00 mL, 3.84 mmol) were added. Then the reaction mixture was warmed up to 80 °C and stirred for seven days. It was quenched by addition of NH_4Cl (7 mL) and extracted with Et_2O (3×15 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (hexane) yielded 390 mg (70%) of the title compound as a colorless oil.

^1H and ^{13}C NMR spectra were in agreement with obtained data for **82**. $[\alpha]_D$ = +8.8° ($CHCl_3$, *c* = 0.91).

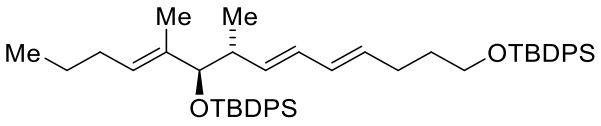
***tert*-Butyl(((1*E*,3*R*,4*R*,5*E*)-3,5-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nona-1,5-dien-4-yl)oxy)diphenylsilane ((3*R*,4*R*)-83)**



In a dry Schlenk flask were dissolved (3*R*,4*R*)-**82** (289 mg, 0.71 mmol) and vinylboronic acid pinacol ester **60** (0.26 mL, 1.42 mmol) in dichloromethane (10 mL). The solution was degassed by bubbling argon. Meanwhile in a heart flask was dissolved the Hoveyda-Grubbs catalyst II (22 mg, 0.04 mmol) in dichloromethane (10 mL) and the solution was degassed by bubbling argon. The catalyst solution was added dropwise to the previously prepared mixture of vinylboronic acid pinacol ester **60** and (3*R*,4*R*)-**82** at 50 °C. The reaction mixture was refluxed for 20 h and then concentrated under reduced pressure. Column chromatography of the residue on silica gel (toluene) yielded 330 mg (87%) of the title compound as a colorless oil.

^1H and ^{13}C NMR spectra were in agreement with obtained data for **83**. $[\alpha]_D$ = −11.4° ($CHCl_3$, *c* = 2.230).

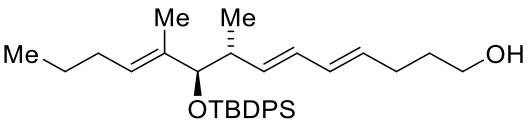
(5*R*,6*R*,7*E*,9*E*)-5-((*E*)-Hex-2-en-2-yl)-2,2,6,16,16-pentamethyl-3,3,15,15-tetraphenyl-4,14-dioxa-3,15-disilaheptadeca-7,9-diene ((5*R*,6*R*)-84)



In a microwave vial were dissolved $Pd(PPh_3)_4$ (31 mg, 0.027 mmol) and iodide **70** (240 mg, 0.53 mmol) in the degassed mixture of THF/H_2O 9/1 (5 mL). Then was added a solution the boronate (3*R*,4*R*)-**83** (296 mg, 0.59 mmol) in the degassed mixture of THF/H_2O 9/1 (8 mL). Then was added TlOEt (80μL 1.17 mmol) with a syringe and the reaction mixture was stirred at 22 °C for 40 h. The reaction mixture was quenched by addition of the saturated solution of NH_4Cl (15 mL) and EtOAc (30 mL). The organic phase was extracted with H_2O (3×10 mL), brine (2×10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue on silica gel (gradient of hexane → 5/1 hexane/toluene) yielded 180 mg (46%) of the title compound as a colorless oil.

^1H and ^{13}C NMR spectra were in agreement with obtained data for **84**. $[\alpha]_D = -23.9°$ ($CHCl_3$, $c = 0.985$).

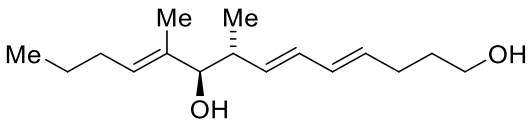
(4*E*,6*E*,8*R*,9*R*,10*E*)-9-((*tert*-Butyldiphenylsilyl)oxy)-8,10-dimethyltetradeca-4,6,10-trien-1-ol ((8*R*,9*R*)-85)



Into a solution of (5*R*,6*R*)-**84** (122 mg, 0.16 mmol) in THF (4 mL) was added TBAF (1M solution in THF, 0.84 mL, 0.84 mmol) at 0 °C. Then the reaction mixture was stirred at 23 °C for 7 days. It was quenched with H_2O (5 mL), extracted with EtOAc (3×3 mL), the combined organic phases were washed with brine (2×3 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexane/EtOAc) yielded 33 mg (40%) of the title compound as a colorless oil.

^1H and ^{13}C NMR spectra correspond with the previously obtained data for **85**. $[\alpha]_D = -35.4°$ ($CHCl_3$, $c = 0.410$).

(4*E*,6*E*,8*R*,9*R*,10*E*)-8,10-Dimethyltetradeca-4,6,10-triene-1,9-diol ((8*R*,9*R*)-6)



Into a solution of (5*R*,6*R*)-**84** (122 mg, 0.16 mmol) in THF (4 mL) was added TBAF (1M solution in THF, 0.84 mL, 0.84 mmol) at 0 °C. Then the reaction mixture was stirred at 23 °C for 7 days. It was quenched with H_2O (5 mL), extracted with EtOAc (3×3 mL), the combined organic phases were washed with brine (2×3 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexane/EtOAc) yielded 8.4 mg (44%) of the title compound as a colorless oil.

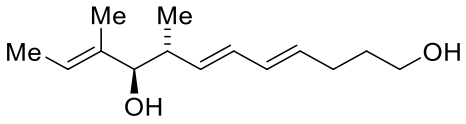
^1H and ^{13}C NMR spectra correspond with the previously obtained data for **6**. $[\alpha]_D$ = +9.8° ($CHCl_3$, *c* = 0.970).[IV]

[IV] Research for the best condition to determine the enantioselectivity was still ongoing process when the thesis was subbmited, therefore it is not covered within this work.

6 CONCLUSION

1. Enantioselective crotylboration in the synthesis of fragments **4**, **5,** and **6** were carried out with the chiral Brønsted acid TRIP-PA **45**. The crotylboration of tiglic aldehyde **61** proceeded with 96% ee and the crotylation of aldehyde **64** with 88% ee.

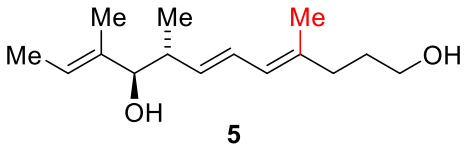
2. Enantioselective synthesis of the E-492 C7-C18 fragment **4** was accomplished in a seven-step synthesis. The key step was enantioselective crotylboration of tiglic aldehyde with *E*-crotylboronic acid pinacol ester **62**. The next step was the cross-metathesis of two alkenes, vinylboronic acid pinacol ester **60** and homoallylic alcohol **71**. In the final step, the Suzuki cross-coupling linked together the unsaturated boronic acid pinacol ester **72** and previously prepared iodide **70**. During the synthesis, the hydroxyl groups were protected with TBDPS protecting group.



4

3. The C7-C18 fragment of actinofuranone A **5** was accomplished by a modification of the cross-coupling partners. Iodide **63** for the Suzuki cross-coupling was prepared by a methylalumination/iodation sequence.

The C7-C20 fragment of JBIR-108 **6** was obtained by crotylboration of aldehyde **64** with *E*-crotylboronic acid pinacol ester **62** followed by cross-metathesis and Suzuki cross-coupling. The starting material was prepared by a four-step synthesis.



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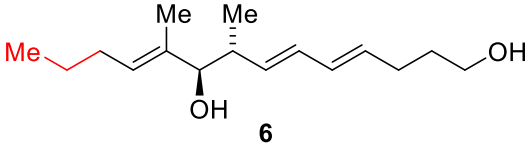

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